Item 507-E-1 HE 20.3202:H99/10
10890

Reprinted from Journal of Behavioral Medicine, Vol. 2, No. 4, 1979
by the National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland 20205

Behavioral Medicine Approaches to Hypertension: An Integrative Analysis of Theory and Research[1]

Gary E. Schwartz,[2] Alvin P. Shapiro,[3] Daniel P. Redmond,[4]
Donald C. E. Ferguson,[5] David R. Ragland,[6] and Stephen M. Weiss[7]

Accepted for publication: July 12, 1979

This article compares behavioral and biological approaches to hypertension, highlights some of the practical, semantic, and theoretical issues involved, and attempts a constructive, behavioral medicine integration of these approaches. The major behavioral approaches to hypertension are described, with a focus on their conceptual limitations as stimulants to research into psychobiological mechanisms. A biobehavioral systems analysis of hypertension is outlined, emphasizing the role of the central nervous system as a common pathway relating environmental and behavioral factors to cardiovascular regulatory dynamics and disease. Schwartz's concept of blood pressure disregulation is discussed, by which behavioral "feedback loops" may be included in the pathogenesis of homeostatic disorders. A detailed discussion of concepts underlying the clinical pharmacological approach to hypertension is provided; parallels are drawn between the conceptual framework and the theoretical and practical questions facing behavioral researchers concerned with hypertension. Synergistic interactive effects of drug and behavioral treatments are proposed. A biobehavioral

[1] This review was prepared by an Ad Hoc Committee appointed and supported by the National Heart, Lung, and Blood Institute, Department of Health, Education, and Welfare. The views expressed herein are those of the authors and do not necessarily reflect those of either the Institute or the Department of Defense.

[2] Departments of Psychology and Psychiatry, Yale University and Yale University School of Medicine, New Haven, Connecticut 06520.
[3] Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261.
[4] Division of Neuropsychiatry, Walter Reed Hospital, Washington, D.C. 20012.
[5] Office of Health, U.S.A.I.D., Washington, D.C. 20023.
[6] School of Public Health, University of California, Berkeley, California 94720.
[7] Behavioral Medicine Branch, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20014.

0160-7715/79/1200-0311 $03.00/0 © 1979 Plenum Publishing Corporation

overview, which links pressor and depressor stimulus patterns to both pathogenesis and therapy, can serve to integrate the previous biobehavioral systems analysis, the conceptual framework of clinical pharmacology, and the notion of biobehavioral disregulation of blood pressure. Implications for future behavioral medicine research in hypertension are provided.

KEY WORDS: behavioral medicine; hypertension.

INTRODUCTION

Recognition of the epidemiological relevance of environmental and behavioral factors to cardiovascular disease, as reviewed by Jenkins (1976a,b), has stimulated a growing interest in the application of behavioral technology to the treatment of hypertension. Animal and human research demonstrates the sizable impact of such factors on blood pressure regulation and on the course of hypertensive disease (A. P. Shapiro, 1971). Their role in the pathogenesis of hypertension awaits confirmation, but recent advances in the behavioral sciences strengthen the theoretical basis for further investigation (Cohen and Obrist, 1975; Miller and Dworkin, 1977).

Of singular importance is research in the last decade concerned with biofeedback and the learned regulation of autonomic nervous system responses (Beatty and Legawie, 1977; Schwartz and Beatty, 1977; Miller, 1978). While initial claims for therapeutic potential were perhaps simplistic, the research paradigm itself has provided a conceptual and empirical framework for documenting measurable plasticity within the cardiovascular system (Blanchard and Young, 1973; Miller, 1969; Shapiro and Schwartz, 1972a). Laboratory rigor has been increasingly applied to demonstrations of learned control of cardiovascular responses in lower animals (recently reviewed in Harris and Brady, 1977) and in normotensive and hypertensive man (reviewed in D. Shapiro *et al.*, 1977; Schwartz, 1977a). Methodological developments are affording more precise understanding of autonomic behavior and promise a means of assessing complex cognitive and social effects on blood pressure regulation.

The pharmacological sciences have likewise advanced significantly in recent years. Hypertension has long been an important research and teaching model for the basic and clinical pharmacologist, whose aim has been to develop rational and predictive means of treatment based on an understanding of pathophysiology. This effort has been increasingly successful, as stated for example by Koch-Weser (1973):

> patients with primary hypertension are not homogeneous in regard to the mechanisms that operate to maintain their excessive arterial pressure. . . . It is increasingly possible to quantitate the importance of these factors in hypertensive patients. We have anti-hypertensive drugs whose mechanism of action is well defined and which can specifically counteract the pressure mechanism.

Thus the pharmacological approach to hypertension is concerned with mechanisms of both the disease and its treatment, with methodology which is analytical as well as evaluative (for instance, pharmacodynamics vs. pharmacotherapeutics). In this way, medicines (or other interventions) themselves have come to be viewed, and used, as *research tools* by which mechanisms may be studied, in turn leading to more refined therapeutic and diagnostic applications.

In a review of the clinical status of behavioral approaches to hypertension (A. P. Shapiro *et al.*, 1977), we noted, as have others (Blanchard and Young, 1974; Blanchard and Miller, 1977; Patel, 1977; D. Shapiro *et al.*, 1977; Frumkin *et al.*, 1978; Taylor *et al.*, 1977), several limitations to the present success of such research. Briefly, in the terms of clinical pharmacology, clinical trials are at an early phase I level, wherein basic physiological effects are observed in patients, without firm therapeutic inferences. Detailed consideration of the various research issues is one goal of the present article. But in discussing these issues among ourselves, we have experienced serious semantic and conceptual barriers to agreement, apparently rooted in heretofore unidentified differences in behavioral and biomedical viewpoints. It is thus our additional intent to highlight and clarify some of the discrepancy and confusion we have experienced, and, by sharing elements of the process of our collaboration, we hope to stimulate in others an effort toward a more integrated behavioral medicine (Schwartz and Weiss, 1978) view of research in hypertension, transcending disciplinary distinctions.

Using hypertension as a unifying example, it becomes clear that the models of pharmacology and the behavioral sciences may be seen to converge broadly. Although pharmacological researchers have in the past confined their attention to biochemical and physiological mechanisms, at the expense of environmental and behavioral factors, the impact of the latter is becoming more and more apparent. "Placebo" phenomena, the subject of rather elegant control and randomizing techniques in drug trials, are nonetheless poorly understood. It is doubtful whether such "randomization" is a correct control, since the "controlled" variables are themselves nonrandom behavioral phenomena (e.g., Stroebel and Glueck, 1973).

Current reviews of drug therapy uniformly omit or truncate discussion of such behavioral phenomena. Benson and Epstein (1975) were critical of the imprecision and disdain *vis à vis* "behavior" tolerated by otherwise careful, analytical scientists and clinicians. They further pointed to the therapeutic relevance of sound patient/physician relationships, which poses special problems currently as techniques of health care delivery change rapidly (see also Lynch, 1977). Finally, there has been an increasing recognition of the importance to public health of the "compliance" of patients to medical regimens; such concern is especially appropriate for hypertension, a disease requiring extremely long terms of management, with drugs producing side-effects as well as beneficial effects, and involving complex schedules and formulations (Nies, 1977). For these and other problems facing the medical researcher and clinician, the collaborative

efforts of behavioral and biomedical scientists can produce results superior to those which either could accomplish alone.

The literature we have reviewed (A. P. Shapiro *et al.*, 1977), purporting to evaluate the clinical effectiveness of various behavioral treatments as applied to hypertension, certainly lacks some of the clarity of intent and method which one finds in the pharmacology literature. If a general criticism of such efforts could be offered, it would be that an expressed recognition of the distinction between empirical observation and clinical evaluation is absent. While data themselves usually pertain to concomittant phenomena (i.e., a treatment and blood pressure change), discussion, speculation, and even reviews are devoted to making a case for (or against) clinical application. This "conceptual leap" is the source of considerable consternation for critics outside the behavioral sciences, especially those who are familiar with premature enthusiasm attending novel treatments.

As Modell *et al.* (1976) put it, a "drug" may be perceived in one of three ways: first, simply as a *chemical;* second, as a *drug,* i.e., a chemical with physiological activity; and, finally, as a *medicament,* a drug which has beneficial, therapeutic effects on a diseased organism. In turn, the "drug" and its interaction with the organism may be *observed, assayed, assessed,* or *evaluated,* depending on the investigative intent and scientific procedure employed, paralleling the three phases of drug trial (see below). This set of concepts involves a continuum of separate, deliberately expressed hypotheses. For instance, a certain drug can be said to have a *toxic action,* a *lethal effect,* and be adjudged *"bad medicine."* These statements obviously are not equivalent; they address distinctly different questions, involving their own determinants and parameters. The pharmacological sciences have evolved terminology and procedures which span the spectrum from analytical to evaluative investigation. Growth of behavioral sciences in the direction of applying techniques to diseases such as hypertension could profit from these insights.

Recent research on the role of the central nervous system in the regulation of the cardiovascular system offers a promise of integrating behavioral and biomedical approaches to diagnosis and treatment of hypertension (Cohen and Obrist, 1975). As stated by Jenkins (1976b), "It appears that . . . psychosocial risk factors may operate through the central nervous system to generate changes in autonomic nervous system functioning and endocrine activity that have an impact upon the cardiovascular system." Following a survey of behavioral treatment models in hypertension, the present article will discuss a view of the central nervous system as a pathway by which environmental and behavioral fa tors may impinge on blood pressure regulation. From this perspective, the biological framework underlying medical/pharmacological approaches can be rationally coupled to the issues and concerns of the behavioral sciences. A discussion of some elementary principles of drug research then follows, with emphasis on their implications for the "biobehavioral" construct proposed.

A number of semantic issues which arise in this context are also identified. The collaboration suggested by the demands of behavioral medicine must go beyond merely physical arrangements; it should generate a conceptual and semantic dialectic. In this way, a basis may be found for formulation of new research problems and issues, leading to and including those of therapeutic applications and treatment interactions.

BEHAVIORAL MODELS OF HYPERTENSION AND ITS TREATMENT

Behavioral approaches to the etiology and therapy of hypertension have, for the most part, evolved from concepts categorically separate from the biological basis of the disease. Hypotheses in this area are couched in psychological rather than biological terms. Descriptions of methods and results reflect little interaction not only with the extensive biological literature of blood pressure regulation but also with the relevent literature in physiological psychology. These limitations illustrate the common operational restrictions characteristic of *any* paradigm, as discussed by Kuhn (1962). Within the broad field of "behavioral approaches," we have identified five narrower categories or models which have been applied to the problem of hypertension (A. P. Shapiro *et al.*, 1977). These paradigms have their own respective orientations, methods, and limitations. The following discussion considers these in detail.

Psychotherapy

Early formal behavioral work in hypertension grew from Alexander's (1939) extension of Freud's psychodynamic theory. Alexander described the typical course of essential hypertension as follows:

> The maturing individual in the course of his life gradually becomes more and more confronted with th complex problems of maintaining his and his family's existence, his social position and prestige. In our present civilization all these tasks unavoidably involve hostile competitive feelings, create fears, and require at the same time an extreme control of the hostile impulses. Those who through constitution or through early life experiences have acquired a greater amount of inhibitions will handle their aggressions less efficiently than others and will tend to repress them. On account of their inhibitions they cannot find socially acceptable legitimate vents for their aggressive feelings, and thus these hostile impulses become accumulated and increase in intensity. It must also be borne in mind that the neurotic individuals who are more than normally blocked in relieving their hostilities and aggressions usually become inhibited also in many other respects, particularly sexual expression. All these inhibitions make them, in their struggle for life, less effective, create feelings of inferiority in them, stimulate either envy, and increase their hostile feelings towards their more successful, less inhibited competitors. These hostilities again require a greater amount of control and thus lead to greater inhibitions, greater inefficiency, and in turn again stimulate hostile, envious and competitive tendencies. (p. 176)

A number of recent studies not only support Alexander's formulation but also provide a psychobiological analysis of the phenomenon (Schwartz, 1977a). In studies by Graham and associates (reviewed in Graham, 1972), data were obtained suggesting that hypertensive patients selectively tend to express feelings of unspecified threat and to assume an attitude of vigilance; further, when the same attitude was suggested to normal subjects under hypnosis, increases in blood pressure were observed. Hokanson *et al.* (1963) have demonstrated that angered, normal subjects experience a pressor effect which tends to be relieved when an overtly aggressive response is permitted. Hypothetically, these results might be explained by sustained isometric tension of skeletal muscles (known to increase blood pressure), with a relative fall in blood pressure associated with the shift to more isotonic muscular activity (Moses *et al.*, 1956).

Cognitive deficits in hypertensives, including an attenuation of perception of affective situations, have also been observed in recent research. For example, Sapira *et al.* (1971) found that hypertensive patients (unlike control subjects) did not report "obvious" differences between two movies, one showing amicable, the other showing hostile doctor-patient interactions. Exploring the neurophysiological mechanisms of such effects, Dworkin and Miller (1977) proposed a novel hypothesis; hypertensives may actually learn to "utilize" blood pressure to activate baroreceptors, thereby inhibiting higher cortical centers in a manner described by Lacey and Lacey (1974). Thus Dworkin and Miller would argue that these individuals might be spontaneously self-reinforcing for hypertension, as a means of attenuating the perception of stressful stimuli; they term such reinforcement as "antihomeostatic" effect. Conversely, it is possible that personality variation could be a *consequence* of the high blood pressure (considered further below) or that both mechanisms may be operative.

Older clinical research was less concerned with the analysis of biological mechanisms. Psychodynamic and supportive therapy was applied to hypertension according to rather simple rationale (Moses *et al.*, 1956). Since anxiety appears to raise blood pressure, relief of anxiety through reassurance and support should help to reduce pressure. Also, if impairment of the ability to handle aggressive and hostile impulses is assumed, dynamic (analytic) therapy might lead to resolution of such conflicts, and hence to blood pressure improvement. Unfortunately, neither systematic measurement of relevant variables nor systematic assessment of improvement was obtained, since the early work was done without controlled outcome methodology.

More sophisticated measurement techniques might be applied to assess this paradigm. For instance, fear and anger may be discerned as distinct psychobiological states by refined assessment of overt facial expression (Ekman and Friesen, 1975; Izard, 1977), or covert facial expression with electromyography (Schwartz *et al.*, 1976a,b). Refined definitions of fight, fright, and flight responses, the study of their differential role in pathogenesis, and advances in the

management of anxiety and aggression through psychotherapy and behavior modification procedures could be combined with potentially important results.

Environmental Manipulation

Another therapeutic approach evolved out of the simple notion that if conditions in the environment are acting as pressor stimuli, then removal of the patient from that environment should lead to a reduction in pressure. This effect has been incidentally noted in a number of studies but has never been systematically examined. For example, hospitalization leads to marked decreases in blood pressure in many hypertensive patients (Moutsos *et al.*, 1967). However, the decreased pressure may also be due to the physical rest or dietary alterations coincident with the hospitalization. In Europe, health spas combined environmental change with relaxation, diet control, and exercise; "cures" are typically transitory in nature.

Relaxation and Meditation

Anxiety-reducing supportive therapy and environmental manipulation have been encapsulated together in the paradigms of relaxation and meditation. Only recently have these techniques received major popular interest and controlled research. The theoretical underpinnings of the several techniques vary greatly, and for the most part have little direct relevance to formal biological concepts of hypertension. One of the early and influential techniques was progressive relaxation, developed in the 1920s and 1930s by Edmund Jacobson (1938). Claiming that patients with high blood pressure often were hypermetabolic and had excessive muscle tension, Jacobson posited that reduced muscle tension would lead to a corresponding decrease in pressure. The latter phenomenon has indeed been reported (Shoemaker and Tasto, 1975), but there has been little attempt to further validate this presupposition. Neither the role of excessive muscular tension in the behavior of hypertensives nor any special responsiveness to relaxation in patients with high levels of muscle tension has been determined.

The most comprehensive analysis of meditation or relaxation procedures has been provided by Benson (1975, 1977). He proposes the concept of a neurophysiological "relaxation response" mediated by the anterior hypothalmus which is opposed to the "fight or flight response" of the posterior hypothalmus. Benson argues that many different religious as well as recreational traditions involve the generation of this psychobiological response and that they all involve (1) a relaxed posture with reduced muscle tension, (2) a quiet environment, (3) simple, quiet repetition of phrases or words, and (4) a passive attitude. Benson's analysis has made a substantial contribution by placing a wide array of methods

within a psychobiological perspective. However, this may be an oversimplification, since different mechanisms and different patterns of relaxation may be discerned (Davidson and Schwartz, 1976; Schwartz *et al.*, 1978). This point will be discussed later.

Placebo Effects

With the "drug explosion" of the last 25 years, considerable concern was directed to "nonspecific" effects of drugs, generally classified as placebo responses. Methodological advances were generally confined to pharmacological research, however, without parallel advances in the behavioral view of such nonpharmacological influences. Those few studies which closely examine placebo effects do report varying degrees of change in blood pressure. But some of the classic studies have methodological faults (Benson and Epstein, 1975). For example, in a study involving use of a "ray gun" treatment for hypertension (Goldring *et al.*, 1956), treatment data were based on the *lowest* blood pressures recorded, while the baselines were *means* of all period values. Still, Benson and Epstein argue that the time has come to do systematic research of placebo mechanisms.

Research on effects of hypnosis or simple suggestions on blood pressure (Redmond *et al.*, 1974) are sometimes still dismissed as placebo effects, rather than viewed as active behavioral processes to be examined in their own right. Similarly, clinicians have long noted the iatrogenic increases in blood pressure produced by taking the patient's pressure (Pickering, 1968). Yet almost no research has applied recent advances in social psychophysiology (D. Shapiro and Schwartz, 1972b) to the placebo problem. Traditional views may be counterproductive, failing to place these phenomena within a biobehavioral context that could stimulate systematic and controlled research (e.g., Schwartz, 1977a; Lynch, 1977).

Biofeedback-Learning

A major impetus toward behavioral treatment of hypertension has grown from the recent behavioral therapy movement in psychology. Behavior therapy evolved from an emphasis on learning theory in experimental psychology, particularly operant or instrumental conditioning. Although classical conditioning procedures were developed by a physiologist (Pavlov, 1927) and were studied in terms of the autonomic nervous system, there was little systematic effort to apply classical conditioning procedures to hypertension. When research in both lower animals (e.g., Miller, 1969) and man (e.g., Kimmel, 1967) demonstrated that operant conditioning procedures could affect responses mediated by the

autonomic nervous system, applications of these techniques to the control of blood pressure immediately followed (e.g., Brener and Kleinman, 1970; D. Shapiro *et al.*, 1970a,b).

The operant conditioning model was originally developed in order to study overt, observable behavior, operationally independent of any underlying processes (Skinner, 1953). Operant conditioning was viewed as neither cognitive nor biological, so that the organism was treated as a "black box." An initial hypothesis was that *any* reinforcer could be used to modify any *voluntary* response (responses innervated by the autonomic nervous system were considered involuntary). With recent work showing the effect of reinforcement procedures on autonomic nervous system responses, it was further assumed that *any* reinforcer could be used to modify *any* autonomic response. This assumption was made without regard to either the mechanisms of such control or the differential limits or constraints on learning (e.g., Schwartz, 1974). These assumptions are now being challenged on psychobiological grounds (e.g., Garcia and Rusiniak, 1977).

The terminology and procedures of operant conditioning emphasize (1) schedules of reinforcement, (2) specificity of conditioning, and (3) directness of conditioning. Schedules of reinforcement involve experimental/environmental variables and parametric manipulations of response/reinforcement relationships and have been systematically explored in experimental psychology. Even so, there have been practically no parametric studies of schedules of reinforcement in the operant conditioning of blood pressure responses.

The issue of specificity in conditioning has involved considerable interest and debate. Since operant conditioning requires that the reinforcer act only on the response(s) receiving contingent reinforcement, it is reasonable to speak about the "specific" reinforcement and conditioning of systolic blood pressure, independently of, for example, heart rate (e.g., D. Shapiro *et al.*, 1970b). However, no distinction is made between a composite parameter such as blood pressure and the individual cardiovascular determinants of blood pressure. The failure to consider underlying mechanisms of what is actually being reinforced produces an immediate biological limitation on operant conditioning *theory* for studying specificity in blood pressure control (Schwartz, 1974).

The issue of "direct" conditioning has similar complications. "Directness" of conditioning means simply that the reinforcers lead to control of the given overt response (e.g., blood pressure) without mediation by some other response. From a biological perspective this distinction is naive and counterproductive (Dworkin and Miller, 1977; Schwartz, 1973, 1974, 1977b). Even operant conditioning of a skeletal motor behavior is not "direct" since it involves some central nervous system process before it is expressed as changes in organ behavior. Consequently, there are numerous possibilities for mediation of operant conditioning in any effector organ.

Other learning paradigms within experimental psychology have been applied to the control of cardiovascular behavior (e.g., Schwartz *et al.*, 1976c).

Lang (1974) and Brener (1974) have emphasized the importance of viewing cardiovascular self-control more as the learning of complex motor skills than as "simple" conditioning. Central to the learning of complex skills is the nature of the feedback the subject receives. The term "biofeedback" is an accurate descriptor attempting to integrate biology and psychology, and emphasizing both physiological feedback and information. In this view, simple binary operant conditioning is the *simplest* of feedback procedures, while more complex, continuous feedback systems are conceptually similar to biological mechanisms. Still, there have been but limited attempts to bring models of homeostasis (Cannon, 1939) and cybernetics (Weiner, 1948) to bear on the learning of human blood pressure. Schwartz (1977a) has presented a model of disorders of homeostasis within a systems-feedback framework. His concept of "disregulation" indicates the consequences that arise when the necessary negative feedback loops are attenuated or eliminated in complex psychobiological systems. This analysis will be discussed in the next section, and represents a departure from the traditional behavioral paradigms and their inherent limitations in interfacing with the biology of hypertension.

Summary

It should be clear from this selective review that no one theory or orientation encompasses all of the potential factors contributing to blood pressure regulation and disease. None is sufficiently biological in orientation to generate systematic exploration of psychobiological mechanisms. Furthermore, no one behavioral theory provides a framework for evaluating behavioral treatments in the diverse subgroups of hypertensive patients. Progress to date has been encouraging, but more integrative models are needed to build the necessary conceptual bridges connecting behavioral phenomena and the biology of hypertension. Current advances in biological systems theory and psychobiology, coupled with an understanding of the pharmacological approaches to hypertension, may help foster this development, and, in the process, help refine the behavioral assessment procedures themselves.

BIOLOGY OF HYPERTENSION: A SYSTEMS ANALYSIS

Systemic hypertension is a disease of disordered homeostasis: the processes that normally maintain blood flow and tissue perfusion in some way go awry. There are myriad ways that the system can dysfunction. A complete understanding of the complex, interacting mosaic of factors involved in normal regulation of pressure would be necessary to determine a "cause" (or "causes") of

hypertension. Space precludes even a partially detailed discussion of the normal regulation of blood pressure; excellent reviews (Korner, 1971; Guyton *et al.*, 1972) cover many of the facets involved. However, for our purpose of discussing the relationship between behavioral and physiological approaches to hypertension, some general comments regarding a "systems view" will suffice.

Figure 1 provides a highly simplified but heuristic view of the levels or subsystems involved in the regulation of blood pressure and the fundamental relationships between the subsystems (from Schwartz, 1977b). Blood pressure (level 1) is a composite of the patterns of determining hemodynamic factors (level 2), each of which in turn is generated by a pattern of peripheral organ activity, or "behavior" (level 3). Such effector behavior is determined by patterns of peripheral neural and humoral mechanisms (level 4), which are expressions of (or regulated by) patterns of central neurogenic processes (level 5). The development of actual anatomical alterations or *organ pathology* (a level 3 effect) is believed to be in part a direct consequence of the sustained high blood pressure (level 1) shown by feedback loop A. Feedback loop B shows how biofeedback for blood pressure (level 1) enters the CNS (level 5). Other feedback loops, as well as various interactions ***within*** sublevels, are not indicated for the sake of simplicity.

The interactions among levels 3, 2, and 1 have been traditionally the province of cardiovascular physiologists. By "mechanisms of blood pressure regulation" (level 1) is meant the particular pattern of hemodynamic factors (level 2)

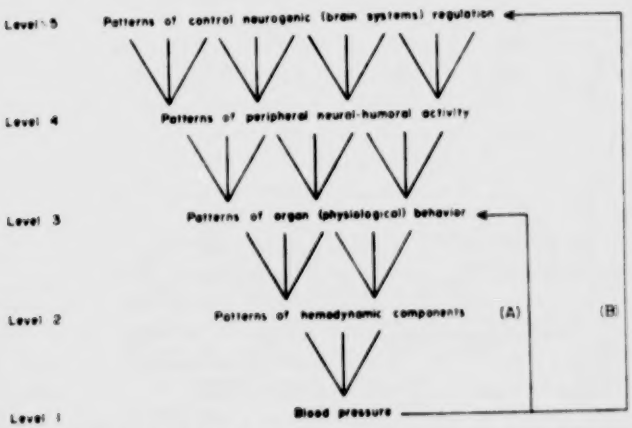

Fig. 1. Behavioral regulation of blood pressure: levels of analysis. Feedback loops A and B represent internal (organ pathology) and external ("biofeedback") effects of blood pressure. From Schwartz (1977b).

generating the pressure in a given instance, and the pattern of effector organ be havior (level 3) responsible in turn. Among interactions (not shown) withi level 3 are those termed "autoregulatory." For example, intrinsic mechanism within the heart directly influence both heart rate and the force of contractio These provide important level 3 to level 2 feedback relationships, contributin stability and "fine tuning" to blood pressure. Likewise, autoregulatory level mechanisms within the kidney and peripheral vasculature contribute to regul tion of local perfusion and may play a role in hypertensive pathogenesis.

Guyton *et al.* (1972) have provided a comprehensive flow chart for suc level 3 mechanisms. However, their discussion of level 4 control of the level mechanism is less complete, and treatment of the complex patterns of CNS sub systems (level 5) regulating level 4 is at best cursory. Omission of level 4 an level 5 mechanisms from detailed consideration is the paradigmatic orientatio of internal medicine and physiology, and partly reflects the limitation of tech niques (including pharmacological, biomedical, and surgical) for specifying lev 4 and 5 processes. Nevertheless, it is precisely these considerations which provid the biological link connecting environmental factors to the regulation of bloo pressure.

The brain is shown as the "highest" level because it is the most comple and integrative of organs; it interconnects and coordinates all the various sen sory, motor, and autonomic organs. In addition, it is physically the farthes removed and thus the least "direct" in the control of blood pressure. Howeve this view is not meant to imply that the brain is the "primary" determinant o blood pressure regulation or that it operates independently of the lower level On the contrary, complex control loops from the lower to higher levels influ ence the behavior of the brain itself. For example, it is known that the brai (level 5) can, via the sympathetic nervous system (level 4), regulate the releas of renin from the kidney (level 3); in turn angiotensin in the bloodstream (lev 1) can influence brain function. Similarly, renal modulation of sodium and wate excretion ultimately influences the brain, while the brain affects both their in take and elimination. A complete description of the regulation of blood pressur then, would involve descriptions *at all of these levels*, including their interrel tionships. In any case, there is ample evidence that the brain cannot be exclude from physiological mechanisms of blood pressure control.

In considering factors such as learning, emotion, and behavior, it is appr priate to begin with the brain (level 5), since it is the primary organ for proces ing and storing information and generating specific patterns of peripheral neur humoral activity (level 4). Patterns of organ activity (level 3) result, which a described in psychological terms as emotion and behavior. The "behavior" the kidneys, as long as they are functionally attached to level 4 processes an thus affected by the brain, is in part always determined by higher neurohumor regulatory mechanisms. However, as mentioned above, the brain's ability to lea and to generate appropriate emotions and behaviors can be influenced by pe

ipheral functions as well (e.g., renal physiology). Thus the modulation of complex human behavior by the function of the kidneys and other effector organs (feedback loops) should not be neglected in applying a biobehavioral perspective.

One advantage of an encompassing, biobehavioral systems framework is that it contains a complete if somewhat simplified "image" of the pathogenic and therapeutic rationales for the varieties of hypertension, whether viewed from biological or from behavioral perspectives. To the extent that elevated blood pressure *per se* (level 1) is causative of the end-organ pathology (level 3) characteristics of chronic hypertention, one should seek the goal, from any perspective, of lowering the blood pressure effectively. This might be done for any level (2-5) of manipulation. If, however, selective defects in physiology at level 2 or 3 account for some morbid clinical effects, as has been suggested by Laragh regarding plasma renin activity (Brunner *et al.*, 1972), then the objective of the behavioral scientist should be to examine level 5 influence on such defects, if any. Likewise, if learning phenomena (level 5) are implicated in pathogenesis (Miller and Dworkin, 1977), the biologist might address the physiological disorder as a consequence rather than a cause of morbidity.

Given the complexity of the nervous, endocrine, and cardiovascular systems, it is not surprising that there are numerous ways in which the systems' feedback mechanisms can and do lead to "antihomeostasis" (Miller and Dworkin, 1977) or disregulation (Schwartz, 1977a). It should be clear that a "cause" at one level can lead to modifications at other levels, which in turn can lead to further disregulation. Thus hypertension can go through stages, where an initial cause(s) of high blood pressure can lead to subsequent pathology such that the *maintenance* of the high blood pressure is due to a second, different mechanism (e.g., Weiner, 1977).

Standard texts in cardiology and hypertension list the numerous etiologies of sustained high blood pressure (Pickering, 1968; Laragh, 1973). For example, renal artery stenosis (level 3) may result in high blood pressure, requiring several systemic adjustments at all levels. These may include a "resetting" of the baroreceptors in the aortic arch and carotid sinus (level 3), with both central and peripheral consequences, the latter including actual damage to the baroreceptors. Damage to the baroreceptors will reduce the brain's sensitivity to blood pressure levels and lead to its disregulation at level 5. This in turn impairs its ability to modulate peripheral neural and humoral mechanisms (level 4) which control specific effector organs, with the goal of returning the pressure to normal levels. Surgical repair of original stenosis may not reverse the course of the disease (Hunt and Strong, 1973), because of the baroreceptor problem or other difficulties (e.g., subsequent damage to the kidney).

Other interactions are possible, and there may be consequences of a more psychological nature. For example, hypertensive patients show cognitive deficits on certain behavioral tests used to assess minimal brain damage (Goldman *et al.*,

1974, 1975). The mechanism for this deficit in humans is not known, but some research suggests that high blood pressure leads to reduction in cerebral blood flow, which may be reversed by lowering pressure with drugs within a certain time. Goldman *et al.* (1974, 1975) have shown that hypertensive subjects whose pressure decreases in response to a behavioral intervention (blood pressure biofeedback) show a corresponding improvement on tests of cognitive function. Although the importance of these measures in chronic hypertension is unknown, high blood pressure, ***regardless of the etiology,*** may influence cognitive, behavioral, and personality parameters mediated by the central nervous system. Furthermore, improvement in these psychobiological processes may result from lowering the pressure, ***regardless of the means by which the pressure is lowered*** (pharmacological, surgical, environmental, or behavioral).

At the same time, it is conceivable that these factors may interact with the disease process and the therapeutic process in another way. For instance, "improvement" in cognitive function may in fact aggravate problems of compliance, since it cannot be assumed that lowered blood pressure *per se* is sufficient "reward" for therapeutically appropriate behavior (A. P. Shapiro, 1960). It is necessary to study such interactions (which is possible only within some inclusive psychobiological systems schema). The impact of behavioral influences on pathophysiology, and *vice versa,* and that of therapeutic intervention on both can be explored with the aim of selecting interventions, or combinations of interventions, most effective from a *global view* of the disease; that is, in terms other than mm Hg and yet appropriate to individual cases.

Expanding on the prior example, a patient with renal artery stenosis (level 3) may have a "fixed" increase in peripheral resistance (level 2) but still show large *phasic* increases in blood pressure. In this case, his baroreceptors may be "reset" due to sustained high blood pressure, and as well he may be "afraid" of his doctor or dislike being sick, activating hypothalamic defense mechanisms (level 5). Without the buffering capacity of an intact baroreceptor system, his blood pressure will be more "labile" or disregulated (Schwartz, 1977a) with large swings and slow declines in response to pressor stimuli from the environment. Thus the first (etiological) factor may actually lead to increases in the second (responsive) factor, which in turn may accentuate the first: a vicious cycle where "hypertension begets hypertension" (Tobian, 1975). Lowering the pressure by surgical intervention may in some cases lead to recovery of baroreceptor function, more stable blood pressure response mechanisms, and a corresponding decrease in behavioral responses to stress. But when the former treatment is impracticable or unsuccessful, *behavioral* interventions might serve to dampen pressor mechanisms, and at least arrest the "vivious cycle" process. But, finally, *combining* environmental and behavioral interventions with surgical and/or pharmacological interventions may be the most selective approach and becomes justified on biobehavioral grounds (Schwartz, 1977a).

Approximately 90% of cases of high blood pressure are diagnosed as "essential," meaning that the pathogenic mechanism cannot be attributed to any known lesion or discrete disease process. Genetic and nutritional factors are clearly implicated by epidemiological evidence (L. Page, 1976). Mechanisms involved include (1) the sensitivity of the vasculature to vasoconstrictive stimuli (level 3), (2) altered production and reuptake of various neurotransmitters or hormones (level 4), and (3) the sensitivity of brain stem and hypothalmic systems resulting in sympathetic overactivity (level 5). Reviews by Reis and Doba (1974), Julius and Esler (1975), Smith (1974), and Esler *et al.* (1977) mention genetic factors as they interact with levels 4 and 5. Behavioral and environmental factors (at level 5) interact with genetic (and nutritional, especially salt) influences at the same level, and it may be that the role of the former in producing and sustaining hypertension cannot be clearly dissected from that of the latter. The nature of this level 5 interaction requires the special consideration of behavioral scientists and physiologists alike.

Julius and Esler (1975) have illustrated how autonomic factors regulated by the CNS (level 5) can play an important role in the development of hypertension. In the early stages of essential hypertension (at level 1), much of the blood pressure increase may result from high cardiac output (level 2); in the later, chronic stages of hypertension, the increase is often primarily due to high peripheral resistance (level 2). Such high peripheral resistance may be caused by structural damage to the vessels (level 3) and thus have relatively little contribution from level 4 and level 5, but high cardiac output seems to be mediated by overactive neurohumoral control at levels 4 and 5.

Julius and Esler define borderline hypertension as a "condition" of elevated blood pressure with readings not sufficiently high to warrant aggressive treatment, that is, "blood pressure intermittently about 150/90 mm Hg, with some readings in the normal range, or minimal persistent pressure elevations, with average readings about 150/90 but below 160/100 mm Hg." As shown in Fig. 2 (Julius and Esler, 1975, p. 687), they hypothesize that the observed abnormalities in borderline hypertension (level 3 and level 2 descriptions) can be explained by neurogenic mechanisms (levels 4 and 5). The present evidence suggests that such level 4 and 5 mechanisms may be involved in over *half the cases* of borderline hypertension.

Those investigators are careful to point out that *not* all borderline hypertensive patients may have heightened autonomic nervous system activity. For instance, borderline hypertensives with high renin levels show evidence of heightened autonomic involvement, while those with normal or low renin levels do not. Thus in the latter cases abnormal pressures are not mediated by activity of higher regulatory mechanisms but rather by disruptions of the "autoregulatory" mechanisms at level 3 itself (Esler *et al.*, 1977). The general implications of these findings for pharamacological as well as behavioral approaches should

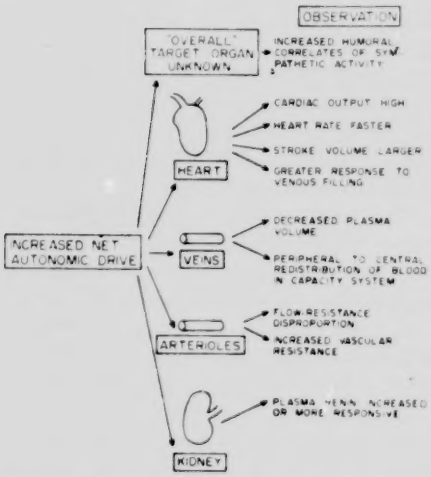

Fig. 2. Neurogenic mechanisms and blood pressure: hypothetical role for autonomic dysfunction in the pathogenesis of hypertension. Redrawn from Julius and Esler (1975, p. 687).

be self-evident. Research that demonstrates differential effectiveness of behavioral treatments as a function of such pathophysiological subgroups has yet to be reported.

Demonstrating heightened ANS activity in subgroups of hypertensive patients does not tell us what specific subsystems within the brain (level 5) are responsible for the increased activity, nor does it tell us to what extent environmental (including cultural and social) stimuli contribute to the increased neural activation at level 5. However, tentative links can be inferred from the traditional analytic literature described above and more modern models of brain function and disregulation (Schwartz, 1977a). Esler *et al.* (1977) have reported that high renin neurogenic borderline hypertensives report suppressed hostility on paper and pencil measures. Two learning/neuropsychological models are consistent with these data. The first (Galin, 1974) concerns the development of a "functional disconnection syndrome" between the left and right hemispheres as a mechanism of repression. Thus, in defensive situations requiring suppression of conscious awareness of negative affect, the left hemisphere allows the right hemisphere to develop a "life of its own." With such a neodissociation of neural systems the verbal left hemisphere reports low distress, while the right, more "emotional" hemisphere would become disregulated (Hilgard, 1973). Data link-

ing right hemisphere function with psychosomatic (Gur and Gur, 1975) and hysteric (Stern, 1977) disorders have been reported.

A second model is based on childhood development, by instrumental learning, of biobehavioral response patterns (Schwartz, 1976). Simply stated, if a child is brought up in a household where the *overt* expression of hostility is negatively punished, the child may learn to *inhibit* the behavioral expression of aggression (level 3) and hold anger in (level 3). The child may also be learning to maintain elevated blood pressure (level 1) *as part of an integrated level 5 response pattern.* Neither model excludes the other. The learning theory description of environmental *development* of a biobehavioral response patterns may be further explained in terms of an underlying level 5 process involving dissociations and disregulations of functional systems (Luria, 1973) in the brain.

These are clearly areas in need of research. The considerations in this section have served to illustrate the formulation of questions regarding the role of various sources of stimulation (both external and internal) in the pathogenesis of high blood pressure. A biobehavioral systems analysis places environmental and behavioral factors in the position of intimate contributors to the mosaic of factors involved in the normal and pathological regulation of blood pressure. It is analysis of this mosaic which can provide the rational foundation for investigating and employing behavioral interventions in hypertensive cardiovascular disease.

FUNDAMENTALS OF THE PHARMACOLOGICAL MODEL: IMPLICATIONS FOR BEHAVIORAL MEDICINE RESEARCH

Introduction

Pharmacotherapeutics, as an applied science, is concerned foremost with *evaluation of therapeutic interventions.* This task of evaluation has been particularly highlighted in the search for effective treatment regimens for hypertension. A biobehavioral systems perspective of hypertension, such as proferred in this review, is readily reconcilable with pharmacotherapeutic models, since a "mosaic" or multifactorial view of hypertensive disease is in large part based on evidence derived from drug research literature. Basic and clinical researchers have become deeply concerned with detailed mechanisms of both disease pathogenesis and drug effects, increasingly confirming that pathophysiology and therapeutics are inextricably and empirically related. This truism permits the distinction between "shotgun therapy" and "rational polypharmacy" and compares with the notion frequently expressed by behavioral scientists and practitioners that specific antihypertensive approaches might be "tailor-made" to individual

patients, on the basis of empirically observed personality or lifestyle factors (e.g., Schwartz and Shapiro, 1973).

Antihypertensive pharmacological agents may be organized according to their loci or modes of action. [For more detailed reviews of pharmacological approaches to hypertension, the reader is referred to articles by Koch-Weser (1974) and A. P. Shapiro (1977, parts I and II), which are addressed to the principles of selective individualization of therapy.] By adapting these principles to the systems schema presented above, sites or modes of action may be related to levels of analysis in the following outline (Table I). While it is beyond the scope of this review to analyze in detail the mechanism of such drug effects, or the secondary and indirect effects of agents across levels (e.g., CNS effects of certain adrenergic antagonists), this simplified outline illustrates the array of therapeutic approaches available and the potential for a mosaic or pattern analysis of pathophysiology.

Since any single agent affects blood pressure by some action *within* a complex, closed system, no agent can reduce blood pressure as its sole, selective effect. In some cases, side-effects sharply limit the utility of a drug. In others, secondary effects, such as the increased cardiac output and sodium retention associated with direct vasodilators, create a requirement for other drugs (B-blockers and diuretics) to compensate for these effects. Finally, since pathophysiological mechanisms are incompletely understood, many response phenomena as yet appear idiosyncratic and the choice of agents and dosage remains to some extent empirical. Nevertheless, the goal of clinical pharmacology remains the objective predictability of effect, and the technical problem of evaluation is inseparable from an analytical approach.

Table I

Drug effect	Drug class	Level
1. Sodium/volume reduction	Diuretic	III
2. Direct vasodilation	Vasodilators	III
3. Blockade of vasoconstrictive reflexes	Adrenergic and ganglionic blocking agents	IV
4. Inhibition of cardiac output	β-Adrenergic blocking agents	IV
5. Inhibition of renin production or release	β-Adrenergic blocking agents	IV
6. Inhibition of CNS vasoconstrictive reflex or drive	Sedatives and tranquilizers	V

Given a focus on problems specific to drug actions and related internal physiological mechanisms, it is not surprising that clinical researchers have in the past usually assumed an exclusionary stance toward behavioral and environmental influences. That is, such "placebo" factors were to be treated as controlled variables, to be carefully "randomized out" in research design. This stance may be argued as historically necessary, in the context of the shift in medicine, within one generation, from empiricism and homeopathy to the "drug explosion" of the 1940s and 1950s, when selective and specific drugs first became available in significant variety. As cited in our earlier hypertension article (A. P. Shapiro *et al.*, 1977), despite whatever theoretical limitations are inherent in this clinically pragmatic position, two important general contributions derive from the approach. First, there was the development and application of methodology by which the clinical value of therapeutic interventions could be reliably ascertained—namely, controlled trial design. And, second, a large body of systematically collected data were obtained, especially regarding hypertension, and important at first only to psychosomaticists, attesting to the relevance of "placebo" factors to health and disease (Waife and A. P. Shapiro, 1959).

With their attention directed toward internal mechanisms, clinical pharmacologists have evolved a methodology and language which, we propose, should be more commonly shared with behavioral scientists concerned with the mechanisms by which blood pressure is influenced by environmental and behavioral factors. If the model and tools of clinical pharmacology are incomplete for the adequate evaluation of behavioral treatments, and if behavioral scientists possess such tools and the willingness to apply them to analytical procedures, then it is particularly critical to build conceptual bridges which might prevent misinterpretations of both theory and scientific intent on both sides. What follows is a *precis* of major terms and concepts used in the evaluation of drugs, applicable to a systems-analytic view of drug effects. Within the following discussion, some of the more obvious conceptual parallels with behavioral science are identified, and others are speculatively mentioned. The coverage of such material is far from exhaustive. The discussion is offered to spur further reflection on these fundamentals, leading, we hope, to a decrease in inadvertent misunderstanding or ambiguity between disciplines and enhance an integrative yet analytical approach to research problems of concern to both behavioral and biomedical researchers.

Pharmacodynamics and Therapeutics: A Spectrum

The phenomena of fundamental interest in pharmacology are drug-organism interactions. In the simplest of schematic views of the paradigm, a drug agent, as a discrete entity, enters into a closed-loop biological system, initiating a dynamic chain of events. This sequence of changes is propagated across all

five levels of organization, and the *interaction* consists of the total set of events consequent to introduction of the drug. Any level of organization may be examined for its own set of particular events, i.e., for parameters of response; any set of parameters may be the selected object of study. The organism's anatomical structure ranges from the atomic to the gross, and the levels of organization range from the molecular to the social; these ranges indicate the breadth of interaction possibilities which might be of concern to the scientist. In actual practice, it is necessary to *specify* or *delimit* subregions of response of immediate interest, recognizing that no study of drug response can be comprehensive. In this way, for instance, a critical distinction is drawn between *pharmacodynamics* and *pharmacotherapeutics*, a distinction which corresponds to different portions of the spectrum of what constitutes drug response.

As mentioned earlier, a drug may be viewed as a chemical, as a drug, or as a medicament. Procedures of observation, assay, assessment, and evaluation parallel the three or four phases of drug investigation and reflect an ascending role of valuation, application, and perhaps, to some extent, subjectivity. The term *response* denotes any portion of the total interaction which is the subject of one of the above approaches; the term is ambiguous unless it is qualified by the frame of reference. A given response may be a drug *action*, defined as an observed change in molecular configuration or cellular function in immediate and proximate consequence to the physical presence of the drug measured in the terms of molecular and microanatomical physiology. But more broadly, *responses* include *effects*, which are the consequences of drug actions occurring across levels of organization, possibly outlasting the actual presence of the drug. The gamut of actions and effects range from the purely physiological to the clinical. For instance, a drug which acts by inhibiting the actions of epinephrine on receptors of the myocardium may have the effect of decreasing the rate and net force of contraction (an observed effect). Consequently, the response of cardiac output to varied stimuli conditions may be depressed (an assayed effect). A resulting *hypotensive* effect may be assessed for use in hypertensive patients, and the drug may prove to have value for its *antihypertensive* effects (i.e., effects ameliorating the disease and its prognosis but not exclusively determined by the hypotensive effect). Finally, the drug may be cheap to produce and dispense, with this economic "effect" bearing favorably in the final clinical evaluation.

The determinants and other terms describing response are similarly spectral, and must be appropriate to the response under study. The *properties* of drugs influencing response may range from molecular weight and solubility to pill color and collar cost. The *characteristics* of the responding organisms include metabolic rate, disease status, color preference, and ability to pay. *Mechanism of response* may be defined as the dynamic, causal sequence of events linking some initiating event with the referent response. Any mechanism is thus a *subset* of the total interaction, with boundaries requiring specification. The commonly used phrase "mechanism of action" should be contrasted with

mechanisms of physiological effects, and mechanisms of clinical effects, depending on the response parameters and determinants in question. Moreover, responses may be considered either *direct* or *indirect*, a qualitative indication of the simplicity, or complexity, of the referent response mechanism. The drug's action is, by definition, relatively direct, as is the cardiac output effect in the previous example. Since "blood pressure" (level 1) is a parameter which is entirely a function of other parameters (level 2-5), a hypotensive effect is *always* indirectly related to drug action, while overall antihypertensive utility is only in part directly related to blood pressure lowering. Finally, except in the context of chemistry, the term *reaction* connotes a physiological effect *countervailing* to some given response; clinically the term may refer to an *adverse* response.

The hypotensive effect of specific drugs is frequently assumed to be the primary if not sole determinant of improvement in cardiovascular function. Actually, only recently have data appeared tending to confirm this supposition, data which remain tenuous for the milder forms of hypertension, and which in any case strictly pertain only to the specific drugs utilized in the reported studies (Fries *et al.*, 1967, 1970, 1972). While the observation of a fall in blood pressure associated with some treatment evokes interest, the effect itself has but limited clinical meaning. The relationship of that effect to long-term value in therapy remains the subject of further research involving different criteria which must be carefully defined. Systematic analysis of response mechanisms should provide clear definitions, within the full continuum of responses and research approaches. In this manner, pharmacodynamics, the study of drug actions and physiological effects, may be contrasted with pharmacotherapeutics, the study of clinical effects applied to the diseased organism. Yet these two perspectives are two sides of the same coin (Goth, 1974), overlapping in their common concern with mechanisms of drug response and pathophysiology, while preserving appropriate conceptual distinctions.

Biobehavioral Considerations

In the first approximation, the "biobehavioral systems model" may be summarized in the same terms as a drug/organism interaction: a discrete "behavioral agent" enters the closed system initiating (by its action) a chain of events (mechanism) which is propagated across all levels of organization, with the interaction manifest as responses (effects) characterized by selected parameters. The model is certainly more complex than that. For instance, the property of "discreteness" is vastly different in its temporal and spatial dimensions. The characteristic of "closedness" of the system differs, since it *includes* the environment; thus one set of *effects* includes change in the properties of the agent. Nevertheless, as an operational analogy, one particular feature certainly holds: the breadth of the spectrum of response. Consequently, the requirements

for careful distinctions among procedural criteria should remain both for an analysis of the gamut of mechanisms and for translations across perspectives.

It is not clear within the behavioral sciences (as they are applied to the problem of hypertension) where lines between "dynamics" and "therapeutics" should be drawn, except insofar as researchers broadly distinguish between basic and clinical research. This latter distinction tends to invite polarization of views, with little precise concern for intervening continua of concept and procedure. The first question to be asked in reviewing current literature on hypertension is whether investigators are (1) observing concomittant phenomena, (2) assaying the effects of specific "agents" in selected populations, or (3) evaluating treatments in the clinical setting. The vast majority of papers appear to involve the initial approach, while their discussion and reviews seem to be concerned with the latter two. That is, the validity of most work seems to reside in the fact that blood pressure changes are related to some treatment or independent variable, while the question of clinical value pervades the background. The nature of the research approach is not explicitly delimited, and perhaps potential clinical value is presumed to "justify" the research. Whatever the case, there is in general a lack of clear and express recognition that the train of causal relationships between the observation and the evaluation of phenomena involves separate hypotheses rather than presumptions.

Another deficiency in current research resides in the very practice of observation: issues of mechanism are avoided, and there is, in a sense, observational "tunnel vision." In spite of the breadth of response possibilities, especially in the behavioral perspective, single parameters or limited sets of response are studied in isolation, rather than in their interaction. There are few data concerned with the *direct* physiological (level 2) determinants of blood pressure (level 1): vascular resistance, central venous volume and return, stroke volume, or regional flow distribution. More *indirect* determinants of blood pressure (levels 3-5) are likewise unexplored, such as intracardiac and peripheral adrenergic nerve modulation, vagal and splanchnic neurovascular mechanisms, renin synthesis and release (Stone and DeLeo, 1976), sodium balance and appetite behavior, and other dietary influences. And in spite of the presumed association of blood pressure change with clinical relevance, the important *effects* of blood pressure change (level 1) on peripheral organs (level 3) are often unobserved: effects on retinal vessels, on renal circulation and excretion patterns, and on myocardial function. Finally, the general effects of treatments, i.e., those not selectively related to blood pressure (which might be considered as "side effects"), remain unelucidated for want of observation. For instance, what are the effects of treatment techniques on ANS activity in general, endocrine and metabolic function, cerebration, sleep, task performance, affect, "lifestyle," etc.? Several investigators have pointed to some of these deficiences in observation (Blanchard and Young, 1974; Blanchard and Miller, 1977; Dworkin and Miller, 1977; Obrist,

1976; Schwartz, 1977a; D. Shapiro *et al.*, 1977) and have reported data with some breadth, however limited (Kleinman *et al.*, 1977; Stone and DeLeo, 1976; Surwit and Shapiro, 1977). Still there remains considerable room for the measurement of response with a sophistication which can provide basic and more precise knowledge of interactions, in turn leading both to an understanding of properties and actions of stimuli (dynamics) and to predictable results in application (therapeutics).

The behavioral model which seems to be tacitly accepted is one of direct agent-action, whereas a blood pressure change is *always* an indirect effect of any intervention. In a previously cited study, if a hypertensive person is shown a movie depicting a doctor/patient relationship, he may show a larger response in blood pressure than the normotensive, either to the movie itself or to a directed interview concerning the movie (Sapira *et al.*, 1971). Although it is appropriate to say that the movie has had an effect on blood pressure, this should not imply that the site of action of such a complex visual/auditory/social stimulus is directly on the pressure. Rather, it becomes apparent that the immediate action is on the sensory input (i) cells of the eyes and ears (level 3i) which via the peripheral nervous system (level 4i) are transmitted to the central nervous system (level 5i) and then back out (o) through the peripheral efferent nerves (level 4o) to the cardiovascular organs (level 3o), producing changed in hemodynamic factors (level 2o) expressed as a change in blood pressure (level 1o). Increased responsivity at *any* step in the chain, or altered activity of various feedback loops, or any combination of such variants peculiar to the hypertensive will be observed as a greater *effect* on blood pressure. Hence the "cause" for the greater effect in hypertensive subjects is neither the stimulus nor hypertension but rather a complex set of circumstances involving various stages or levels of organization. Furthermore, the nature of the stimulus, which may be well defined in terms of physical dimensions (frequency, intensity, du. tion) may yet be poorly defined in the absence of observation of action and mechanisms of effect. Especially within the operant conditioning approach, properties of stimuli are unclear at least to the same extent that all responses are interpreted as if they were *actions* of stimuli.

The "mediation issue" has been discussed extensively in the past, but in the same context of observational limitations on analysis it seems insoluble and perhaps makes little sense (Crider *et al.*, 1969; Katkin and Murray, 1968; Katkin *et al.*, 1969). When investigators speak of "direct" operant conditioning of blood pressure, they are explicitly implying that no other *observable* response is intervening or mediating in the effect. This notion is on its face absurd: the better word is *observed*, indicating not the absence of a response but rather the absence of appropriate research effort to make the observation. Likewise, when "indirect" operant conditioning of blood pressure is said to be mediated by, for example, changes in muscle tone, the precise actions and effects of stimuli leading

to reduction in muscle tension, and from muscle tension to blood pressure, are ignored. Both cases belie the complexity, and indirectness, of the psychophysiologic pathways involved. Perhaps the mediation issue is resolved most rationally by the term *mechanism* (Schwartz, 1974) followed by meticulous description of such pathways (see Cohen and Obrist, 1975; Dworkin and Miller, 1977).

Definition of response as an action, effect, or integrated set of actions and effects is broader and more cohesive than traditional behavioral concepts of "response," which typically refer to some overt change, or inferred covert change, without regard to its underlying biological substrate. Distinction in the behavioral sciences among behavior, physiology, and subjective experience as three interrelated sets of responses (Lang, 1971; Borkovec, 1977) is a beginning step in breaking a total response into its underlying components. Unfortunately, the classic mind/body dualism and the traditional notions of behaviorism are sustained, implying that behavior is *not* physiological or that the mind is a response system separated from physiology. However, to the extent that motor behavior and subjective experience are products of (or mediated by) the central nervous system (Luria, 1973), it becomes more appropriate to classify "overt" motor response, "covert" visceral response, and subjective response all in terms of a physiological response system (Schwartz, 1977a,c, 1978). This more cohesive view of response phenomena, while permitting an analysis of its segments, in the very least offers a broader basis for conceptual and semantic rapport between behavioral and biological scientists.

The essence of such a view of response lies in the delineation of mechanisms, that is, the linkages along the mind/body contiuum, across the various levels of effect which interest different disciplines. In such areas of behavioral science as information-processing theory (Norman, 1976), the term *mechanism* is used explicity to express stages of response within the underlying cognitive substrata, and implicitly to express stages of response within the underlying neural and humoral substrata. Such usage has yet to find its way into the clinical literature, and has not been applied to the evaluation of behavioral treatments, especially in hypertension (Schwartz, 1977a). Since psychoanalytic theory was evolved from biological tradition (Pribram and Gill, 1976), the role of regulatory mechanisms in related theories of personality has been considered important by psychoanalysts; however, their substrata have been purely hypothetical constructs, neither observable nor provable. Operant learning theory has generally disregarded intervening steps between environmental stimuli and overt response, and previous behavioral theories have tended to be purely descriptive (Powers, 1973). But where the process of research is aimed toward *evaluation* of behavioral treatments of an illness (hypertension) in which several segments of the psychophysiological structure have been or can be mapped out, the objective across disciplines must be to achieve commensurable views of such concepts as "response." This indicates a need for greater emphasis on existing or developing

psychobiological perspectives, supported by systematic analysis of mechanisms, with the sort of crossover among relevant approaches advocated by Cohen and Obrist (1975).

One recurring issue in the critical literature underscores several of the points in the foregoing discussion: how "significant" are observed changes in blood pressure? In the previous review concerned with the clinical status of nonpharmacological methods of treatment (A. P. Shapiro *et al.*, 1977), effects were tabulated in terms of the magnitude of blood pressure responses. A fairly wide but clinically unimpressive range of change has been reported with the various treatment techniques, with a variety of schedules and methods for measuring blood pressure represented by these several studies. Most reviewers point out that the limited magnitude of blood pressure results obtained so far is of the same order of magnitude as various nonspecific effects, e.g., placebo, and that such changes, in any event, are of doubtful clinical relevance.

Such results have led to several suggestions for "improvement" of results, all of which seem pertinent. First, further refinement in methodology for measurement of blood pressure is required, and various measurement systems should be appropriate to the research objective. For instance, it is clear that beat-to-beat tracking of blood pressure is critical to observing acute responses within the laboratory, so that basic dimensions such as the properties of treatments, phenomena such as "shaping," and neurophysiological and humoral concomitants can be studied with precision. On the other hand, frequent but intermittent records, taken outside the laboratory for prolonged periods, would seem to provide data reflecting clinical effect, as exemplified by the approach of Patel (1977) and Kristt and Engel (1975). Furthermore, as discussed above, approaches based on a broader array of measurements of response are required. Since results are uniformly expressed as "change in blood pressure," more precise design of baseline, control, and crossover methodologies is necessary (e.g., Surwit and Shapiro, 1977). Means for identifying and characterizing individual subjects according to response magnitude (or lack of it) are also desirable. The central concern of all these issues is the fact that in general, across the various studies of the various techniques, the magnitude of blood pressure change is "small," and, as is frequently stated, the results to date are "disappointing." While such discussions and suggestions have been useful, it would seem that the orientation of critic and investigator alike involves a quantitative leap in conceptualization.

Blood pressure, the parameter, has taken upon itself extraordinary *value*, for researchers, clinicians, and patients. This rather coarse index of function in a highly complex system is equated with health and well-being on the one hand, and with the success of research on the other! To a considerable extent, the history of the pharmacological approach to hypertension has played a role in the ascription of such ***a priori*** value. Such valuation certainly affects the choice of parameters in research, and, more, confuses the intent, hence procedure, of in-

vestigational design. Of at least equal importance, it impairs communication with other scientists who do not share the valuation. For the observer of precise physiological mechanisms, blood pressure is but an indirect and crude measure of any response. For the evaluator of therapy, blood pressure is an equally crude though useful measure of clinical benefit. From either viewpoint, the relationship of blood pressure to the biobehavioral interactions of interest is hypothetical, at best worthy of further research. However useful in clinical practice, this parameter might do well to recede to a more appropriate position within a general psychobiological framework, both in terms of the physiological pattern of response and in the spectrum of research perspectives. As a consequence, it is suggested, the question of enthusiasm vs. disappointment (Miller, 1975) might not arise.

Dose-Response Relationships

The central technology of pharmacology is the study of the relationships between the *dose* of an agent (drug weight administered per unit time for stated duration) and the magnitude of the observed *response*. There is generally a graded (if nonlinear) relation between the two quantities. A great variety of "typical" relationships exist, the peculiarities of each often related to particular pharmacodynamic mechanisms. Nevertheless, for the purpose of this discussion, an idealized representation of the sigmoid dose-response curve (see Fig. 3) serves to illustrate two general but critical sets of issues. The first of these is concerned with the definitions of the technical terms *potency* and *efficacy*, which in their colloquial usage may lead to conceptual ambiguity. The second has to do with *limitations*, the consideration of which provides quantitative details of agent properties, organism characteristics, and response mechanisms.

Referring to Fig. 3, the curve indicates three features common to most dose response relations: (1) a *dose threshold* or minimal dose below which response does not occur, (2) a region where *direct relation* between dose and response occurs, and (3) a *maximal response*. *Potency* is the dose required to yield a given response; thus *relative potency* involves a comparison (assay) of two or more drugs, expressed as the ratio of respective doses for an equivalent response. Note that the referent response requires specification, i.e., it represents a single point on the dose-response curve of each drug. Thus two drugs may be equipotent for a maximal response but vary widely in terms of threshold and slope. Furthermore, since the quantity "dose" refers to both weight and *schedule*, relative potency statements may differ widely between comparisons of single dose and chronic administration. *Potency* is rarely a clinically useful term. For closely related drugs, it may merely affect the size of the pill. On the other hand, drugs equipotent by weight might be quite dissimilar in their schedule of administration (one feature of cost/benefit). A statement of potency is,

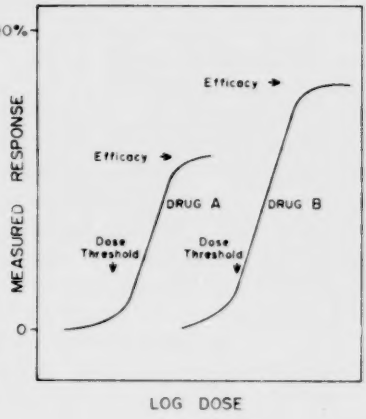

Fig. 3. Dose-response curves. Two drugs with different potencies (that of B less than that of A) and efficacies (A less than B) are shown, for a given hypothetical response. Clinical effectiveness is not necessarily determined by this comparative assay technique (see text).

as well, specific to the response (usually some physiological effect selected for presumed clinical value), which is the subject of assay. Relative *clinical potency*, the dose required for a given clinical response, may be most difficult to determine, since a clinical response consists of a total *set* of therapeutic and toxic effects. Drugs equipotent for hypotensive effect, but not for toxic effects, are not clinically equipotent. Consequently, any offhand statement that a certain drug (or behavioral treatment) is "potent" is fraught with ambiguity.

Efficacy is, simply, the maximal or ceiling response defined by the dose-response curve, beyond which increased dosage has little increased effect. *Relative efficacy* relates two or more drugs according to response maxima. As a quantity, efficacy is neither determined by potency nor determinate of clinical value; rather, it is a property of the drug in its own right, and, as with potency measurements, the response is specific to the given assay. Furthermore, the given response is not necessarily a positively valued one, since a drug may be relatively efficacious for toxicity. *Clinical efficacy* again refers to a total set of effects, without prejudging the value of any given effect. Defined thusly as a quantitative term, it is clear that the colloquial use of "efficacy" is an ambiguous one, which usually presupposes a desired therapeutic response which either occurs or doesn't occur. *Effectiveness* has been suggested as a generic term for the balance of cost and benefit of therapeutic applications. Thus a drug with hypotensive efficacy greater than other drugs may or may not be more effective in hypertension. Effectiveness is largely determined by the efficacy for *positively valued* effects but may be reduced to zero by efficacy for adverse effects long before the actual "ceiling effect" is realized by maximum dosage.

Biobehavioral Considerations

Aside from such semantic considerations, a model based on precise study of dose-response relationships poses several important challenges to the behavioral sciences. The first of these, and not the least important, is the problem of quantification of *dose*. The complexity of environmental and behavioral treatments places major limitations on such technology. However, it must still be considered a *conceptual* goal, especially where comparison of behavioral and pharmacological treatments is the subject of research. The parameters by which treatments are defined clearly need refinement. At present, no proposed therapy is adequately defined such that some minimum dose threshold, some maximal response, or gradations of dose-response can be ascertained.

These comments presume that blood pressure is the dependent variable of response in dose-defined assays. The imprecision of this measure (BP), both mechanistically and clinically, has been discussed above; *response* quantification still needs refinement as well. The present state of the art in assay of behavioral treatments appears to be the binary presence/absence of some treatment (dose), with continual measurement of blood pressure change. The tendency is to judge relative potency by comparing the magnitude of response to different treatments, to presume that efficacy is the sole determinant of effectiveness. However, all differences and similarities among responses to treatments may be accounted for, hypothetically, by "dosage" differences, which in all cases may be submaximal. In the sense of these words used here, present technology indicates that such terms as *potency* and *efficacy* are used, at best, imprecisely.

It would seem that those familiar with studying the parameters of learned behavior could contribute considerably to translating the determinants (or properties) of defined treatments into the notion of "dosage." The concepts of threshold stimuli, rates of stimulus delivery and response acquisition, peak response, shaping, and stimulus optima are applicable. Of particular relevance to behavioral theories are the frequency of visits, amount of practice outside of the therapy session, and duration of a given practice period. Various techniques might thus be compared within themselves, parametrically. Relaxation methods, for instance, might be studied according to the intensity (amplitude and duration) of the treatment procedures itself, rather than by some measure of response (e.g., skeletal muscle activity presumed to reflect dose). Biofeedback techniques are particularly amenable to precise parametric analysis, including the timing and amplitude of feedback and reinforcements. If comparison of effects within treatments can be achieved, then efficacy phenomena would become demonstratable. For instance, as meditative techniques are increased toward a maximal blood pressure response, any negative consequences might be ascertained which might limit effectiveness: hypotension, lethargy, cognitive deficits, narcolepsy. The distinction between behavioral efficacy and behavioral effectiveness for the given therapy would thus become clearer. Consequently,

relative potency, efficacy, *and* effectiveness might then be determined *across* treatments. Whereas recent studies (such as Surwit and Shapiro, 1977) are a promising beginning toward comparisons of the latter type, they lack the fundamental dose-response relationship data required for full treatment assessment.

As mentioned earlier, an important feature of the dose-response relationship is the *limitations* on that relationship — those imposed by the properties of the drug *and* the characteristics of the organism. *Dose limitations* may occur simply because the physical size, volume, or schedule of dosage becomes impractical to administer, at some point prior to maximum response. Dose may also be limited if an action of the agent becomes toxic before the reference response is maximized. *Response limitations* may likewise occur because of physical restraints, which in the case of drugs may result from a "saturation" of the response mechanism, or because of some rate-limiting step in the sequence of effects. The referent response itself may become toxic. Any countervailing (or homeostatic) effect of the referent response may become equipotent to the response.

Such limitations compose the body of constraints which bear on *any* treatment-organism interaction. Treatments should be considered in these terms, not only in the sense of the physical dimensions of a therapeutic approach (which may bear upon cost/benefit analysis) but also in terms of the *mechanism* of such constraints. In short, *why* does the response of blood pressure to different behavioral strategies seem to be limited in most cases? In the exceptional cases, why aren't these same limits observed? Or, stated another way, to the extent that predictions of effects associated with relaxation, learning, or biofeedback theories fail, the exact nature of psychobiological constraints may be revealed (Schwartz, 1974).

Characteristics of the Organism

Several features of the individual responding organism are determinate of the magnitude of the given response and of the limitations of response. Consideration of some of these is helpful in accounting for individual variations, and, clinically, in optimizing the drug response. The term *responsivity* refers to the relative magnitude of response for a given dose, in an individual or species, and corresponds to the concept of potency. In the diseased individual, responsivity is usually taken to refer to positively valued (therapeutic) responses (as opposed to reactions) to these actions or effects. For this, Goth (1974) uses the word *susceptibility*. Varying across individuals, it is recognized that responsivity is affected by various pharmacodynamic *characteristics* of the organism: (1) absorption, metabolism, and excretion of the drug, i.e., transportation of the drug molecule to and from the site of action; (2) *responsiveness* to the drug at the loci of action; (3) tonus of *antagonistic factors* influencing the response mechanism, i.e., the *resistivity* to change; and (4) reserve or capacitance of the homeostatic

system, or *reactance* to change. Variation in such characteristics alters both the slope and the threshold of the dose-response curve, and imposes limits to the magnitude of response. These characteristics are in turn influenced by such factors as (1) age, sex, weight; (2) genetic factors; (3) nutrition, (4) metabolic rate; (5) pathological state; and (6) prior exposure to the drug (e.g., the concept of *priming* and *maintenance* doses).

Several terms are used to describe specific variations in responsivity. *Tolerance* is an *acquired hyporesponsivity* occurring continuously and gradually over an ascending range of dose. *Tachyphylaxis* is rapidly acquired hyporesponsivity occuring with initial dose. *Hyperresponsivity* implies a low threshold and increased slope of the dose-response relationship. Clinically, this is the same as hypersusceptibility. *Reactivity* is responsivity for effects *countervailing* to the response in reference or *adverse* effects. *Hyporeactivity* and *hyperreactivity* correspond to tolerance or hyperresponsivity for such reactions. Clinically, these apply to toxic effects. Idiosyncrasy or *metareaction* is an unusual reaction which is pharmacologically unpredictable. *Sensitivity* refers to *immunological* response and may be a metareaction.

Biobehavioral Considerations

The general notion of responsivity, its qualities, its determinants, and its mechanisms, may well be critical to successful application of behavioral methods to such physiological disorders as hypertension. The responding organism may be viewed, as described above, as a system containing a set of factors which influence response mechanisms. Some of these factors augment and some antagonize the occurrence of any given response. Such factors vary from individual to individual, and the set of factors determines the nature of the response in a given individual.

Until recently, little serious attention has been given to the "pharmacodynamics" of environmental and behavioral factors which influence individual responsivity. At the simplest of all levels, pill-taking behavior, or "therapeutic compliance," has profound effects on the absorption and metabolism of drugs, since noncompliance results in nonabsorption and nonmetabolism. Less whimsically, one may postulate that such factors do indeed enter and act on the central nervous system (level 5), and do compose part of that set of factors which *modulate* responsivity. The mechanisms involved are not all clear, but the validity of such a view has firm evidence in the literature of pain therapy and psychopharmacology. Psychological events can "override" the effects of hypotensive drugs, and few drugs effectively blunt responsivity to psychological pressor stimuli, although certain drugs may modify the mechanisms of the pressor response (Goth, 1974). Equally intriguing is the early evidence (Goldman *et al.*,

1974, 1975) that pressure levels *per se* (or related hemodynamic factors) may directly affect cognitive function, thus modulating responsivity to the action of environmental factors. And finally, other data would indicate that *learned inhibition* of reception or processing of psychological noxious stimuli influences the pattern of responsivity, conceivably to drugs as well as to pressor stimuli (Sapira *et al.*, 1971).

Clearly such factors are critical to investigating and optimizing the effects of behavioral therapeutic modalities. Several parallels may be drawn between the pharmacological schema and the biobehavioral model in this regard, outlining potentially fruitful areas of investigation. *Historical and epidemiological terms such as age, genetics, race, nutritional history, prior learning experience, personality, and even culture can all potentially be translated into the underlying biological subsystems that they have presumably modified.* The *prior* history of a person might thus influence the *present* responsivity to a given drug or environmental agent, albeit in a complex manner. Furthermore, the pharmacological concept of tolerance closely parallels the behavioral definition of learning, particularly the psychobiological concept of habituation, which is often defined as an *acquired hyporesponsivity* to a stimulus that occurs over time. Habituation (a learned response) can be distinguished from simple fatigue or response decrement over time. That patients may lose interest in practicing certain self-regulatory procedures is one example of a possible tolerance effect in behavioral treatment. Finally, in the behavioral literature, a form of hypersusceptibility (referred to by behaviorists as heightened suggestibility) has been hypothesized to occur during certain treatment conditions. Recent research (reviewed in Suedfeld, 1975) suggests that 24 hr of sensory isolation leads to enhanced retention of self-regulation procedures involved in the control of smoking and eating behaviors. The effects of sensory deprivation can be described as producing a relative hyperresponsivity to specific environment agents. Another illustration is provided by Budzynski (1976), who has used biofeedback procedures to induce low levels of physiological arousal as a means of increasing a person's susceptibility to verbal and cognitive self-control strategies. However, without parametric studies to generate behavioral dose-response curves for sensory deprivation or biofeedback, more precise documentation of these susceptibility phenomena is lacking.

Thus two general areas of further work are indicated. First is the systematic study of the epidemiological factors associated with variance in response across individuals, particularly those related to hypertension. The considerable body of work concerned with the "hypertensive personality" or style, mental processes, social functioning, etc., peculiar to the diseased person should be investigated *vis à vis* response vectors for both drugs and behavioral treatments (A. P. Shapiro, 1960; Weiner *et al.*, 1962; Richter-Heinrich *et al.*, 1975; Stratoudakis *et al.*, 1976). Second, research should be concerned with the inter-

action of factors influencing responsivity, for identification of the mechanisms by which responsivity is modulated. Thus treatment strategies should not merely aim to alter some physiological output (blood pressure), but to alter or optimize characteristics of organism determinant of the quality of the response to primary stimuli (including drugs).

Selectivity

The physical properties of a drug agent, of course, determine its route of administration, the size and schedule of dose, and, in terms of molecular or chemical activity, its potency and efficacy for action. A singularly important property, important here for its semantic implications, is the property of *selectivity*. First, no drug is known which is truly *specific* in producing a single, all-exclusive action. Selectivity describes the *breadth* of the total *set of actions and effects* produced by the drug, independent of the *clinical value* of the subset of clinical responses (referent) within the set. In other words, the term *selectivity* applies to *all* drugs — different drugs have different selectivities in the sense that *each produces a unique set or pattern of actions and effects.* If that set happens to be a narrow range of effects, and those effects happen to be relatively direct in ameliorating a given disease, then the drug is said to be *selective*, and *relatively specific* for the disease. In this context, the term *specificity* is indeed a relative one, laden with the value placed on the designated and desired response. Pharmacodynamically, "specificity" is a dubious entity and any claim that an agent has a *specific* effect, especially when that effect is an *indirect* one (such as blood pressure), may be viewed askance.

Biobehavioral Considerations

In the behavioral sciences, selectivity is often used in a more simplistic fashion to imply *selective* control over a *single* response. However, as discussed earlier, and illustrated in Fig. 1, the distinction between *specific* control vs. *pattern* control is an oversimplification and emphasizes a false dichotomy. For example, "specific" control of heart rate (level 3) can actually involve differential *sets* or *patterns* of underlying peripheral, neural, and humoral mechanism (level 4) (Schwartz, 1977b). Furthermore, "specific" control of heart rate in the behavioral sense would imply that *no* other overt or covert response was also simultaneously controlled, a highly unlikely event.

The research necessary to document whether changes in blood pressure produced by various behavioral procedures reflect common mechanisms is only in the beginning stages. Although similar decreases in blood pressure may be ob-

served (level 1's are similar), the pattern of hemodynamic effects may be different. For example, level 2 selectivity for blood pressure biofeedback may produce larger changes in peripheral resistance than cardiac output, while level 2 selectivity for Benson's relaxation procedure may produce larger changes in cardiac output. If future research should obtain these results, this would imply differences in the set or pattern of level 3 changes in the cardiovascular system. On the other hand, if research determined that overall peripheral resistance was similar in these two instances, it could still be the case that the *patterns* of change were different [i.e., regional differences in resistance effects (level 3)]. By systematically examining changes in other response systems (e.g., changes in skin resistance), it is possible to further determine the similarity and differences in selectivity between these behavioral techniques.

Benson (1975, 1977) claims that a hypothetical (level 5) relaxation response results in decreased activity over much of the sympathetic system (both neural and humoral — level 4). Hence he would predict that his procedure produces greater decreases in sweat gland activity than biofeedback for blood pressure, a prediction shared by other authors (e.g., Davidson and Schwartz, 1976). Although the available evidence favors greater selectivity for blood pressure biofeedback than Benson's procedure (Kristt and Engel, 1975), this research is still incomplete.

The notion of selectivity has implications in terms of the use of combinations of agents therapeutically. In the pharmacotherapeutic approach of hypertension, different combinations of drugs are often given in order to produce *selected* combinations or patterns of actions and effects. To conduct systematic research on the question of combinations of treatment, it becomes necessary to define the *precise* selectivity of different behavioral treatments (describing their actions and effects at the various levels throughout the cardiovascular system and across other systems) (Schwartz, 1977a).

Finally, the selectivity issue relates to *diagnosis* as well as to treatment of hypertension. The concepts of response pattern and selectivity require that other, noncardiovascular systems be assessed as a means of determining the total pattern of clinical problems in the individual. It follows that a comprehensive psychobiological assessment would include the pattern of environmental and behavioral factors contributing to the total set of problems exhibited by a given patient (of which hypertension may be only one subcomponent). Practitioners of behavioral therapy whom these authors interviewed uniformly discussed the art and practice of "tailor-fitting" treatment programs to their individual patients. Implicit in such an approach is recognition of both the factors affecting variance in individual responsivity and the selectivity of treatments, such that the approach "fits." Such considerations currently have intuitive validity, but await experimental confirmation and precise description (Davidson and Schwartz, 1976; Schwartz *et al.*, 1978).

Drug Interactions

Drug interactions are defined as the combination of two (or more) drugs resulting in a ***new set or pattern of actions and effects.*** In ***homergic interaction,*** responses are identical, yet the response mechanisms *may* or *may not* be the same. Thus at one level (e.g., level 1) the same response may be observed, yet the pattern of hemodynamic factors at level 2 may be different. As mentioned above, this distinction is not typically recognized in the behavioral sciences. Among homergic phenomena, ***summation*** of effects occurs where the mechanisms may or may not be identical, while the term ***additive*** implies mechanisms are identical. In this sort of interaction, no change in respective potencies or efficacies are observed with the interacting drugs.

Heterergic interactions involve *different* responses for each drug; the actions and mechanisms are of course different. Such interactions are called ***synergistic*** when the combined response is greater than the sum of the independent responses. In synergism, an increase in potency or efficacy occurs because one drug affects ***responsivity*** or ***reactivity*** to the other drug; this effect is also called *potentiation.*

Antagonism occurs when there is a decrease in potency or efficacy as a result of combining two drugs. There are four different types of antagonism: (1) ***functional antagonism,*** where different responses may be countervailing to each other (*negative summation*); (2) *competitive antagonism,* where the drugs may compete for the same receptor (*negative additive effect*); (3) *physiological antagonism, noncompetitive,* where one drug may effect responsivity or reactivity of the other drug (*negative synergism*); and (4) *chemical antagonism,* where drugs actually chemically react with each other.

This range of qualitative interaction possibilities complicates the usual concerns for dose-response, characteristics, and properties. Research designs must consider (1) the components making up the multiagent package, (2) the individual sets of action and effects, and (3) the specific ways in which the agents interact to produce unique sets of actions and effects. Problems of *interaction* can apply not only to drug/environment or environment/environment interactions. The latter cases serve to reemphasize all the discussion up to this point.

Biobehavioral Considerations

Until quite recently, the concept of interaction was viewed in the behavioral sciences primarily in a statistical sense as an interaction term in the analysis of variance. Interactions were often seen as problems because they required the development of more complex models than the single-variable, "either-or" model. The researcher in behavioral medicine must thus consider the fact that

A plus B may give results that are quantitatively and qualitatively different from the properties of A or B alone (holding one constant while manipulating the other) (e.g., Schwartz, 1975, 1976, 1977b,c). Applying the concept of multiple, interacting drugs or agents to environmental and behavioral treatments, it becomes immediately apparent that the social and behavioral environment can be viewed as a complex "capsule" consisting of many separate drugs or agents administered in a package.

Again referring to a movie example, the set of factors making up the total social environment will include (1) the social *setting* – is the person alone, or are two or more people present; what types of people are present? how do they look? how are they acting? what are their nonverbal (visual) cues? what is their verbal resonance (both in language and in affective tone?); (2) the set of auditory and visual stimuli present in the movie – does the film have a sound track? is there music present? what type of music? what is the specific content of the picture? is it in color?; (3) the physical setting – noises from outside the theater, the temperature of the theater, the odors in the room, plus other atmospheric effects such as pressure and electrostatic changes that can affect the processing of the central nervous system; and (4) the presence of "drugs" (alcohol, popcorn) which affect the response to stimuli. Such an environment is similar to a capsule containing a complex pattern of stimulation affecting different central processes and peripheral processes. Regarding blood pressure, this environment may be described as consisting of complex combinations of pressor and depressor stimuli. As the central nervous system (level 5) receives and processes the stimulations, it yields a set of effects which filter down to lower response levels.

A similar interaction approach can be applied to instructional and behavioral treatments. As previously discussed, Benson's relaxation response procedure is actually a complex multitreatment package that not only manipulates patterns of stimulation in the external environment (withdrawal to a quiet, peaceful place) but also involves the regulation of a *pattern* of internal events involving relaxed muscles, breathing, auditory stimulation, and inhibition of "extraneous" external and internal stimuli. These general elements of the interaction might be analyzed according to their neurophysiological components, which then can be viewed as *individual* agents or treatments. Each can have its own *set* of actions and effects. However, *together* they combine to reproduce a unique set of actions and effects, which Benson has labeled as the relaxation response (see Davidson and Schwartz, 1976).

A final example of behavioral treatment interactions concerns the combination of classical and operant conditioning procedures. It is now becoming recognized that from a biobehavioral point of view organisms are "prepared" to make certain associations with some environmental stimuli and "contraprepared" for others (Seligman, 1970). Schwartz (1974) suggested that "reward"

constraints from unconditional responses would interact with instrumental learning of cardiovascular responses. A study Bouchard and Corson (1976) illustrates this interactive effect in biofeedback for heart rate: differential unconditioned effects on heart rate of gaining or losing money interact with the capacity to voluntarily increase or decrease heart rate. In addition, it is likely that the neural mechanisms of operant visceral learning are not identical to those of classical conditioning. For instance, DiCara and Weiss reported that decorticated rats could learn a classically conditioned heart rate response but not an instrumentally reinforced one (e.g., DiCara and Weiss, 1969). Consequently, it follows that a biofeedback package probably includes a combination of instrumental and classical components, which should be recognized and systematically studied. Recent studies are a step in this direction (Furedy and Fajner, 1976; DeGood and Adams, 1976; Elmore and Tursky, 1977).

Dissecting such complex behavior into their underlying psychobiological components has the advantage of making it possible to *compare* different behavioral treatments in "pharmacological" terms. Certain individual subtreatments may be shared in common (deliberately or inadvertently) but to different degrees (i.e., with dosage differences). Others may be unique to one and not the other treatment. In either case, interactions with other components may be additive, synergistic, or antagonistic, resulting in selectively different patterns of response for different treatments.

The concept of synergistic interaction, from a biobehavioral systems perspective, has one more especially important implication. That is that drugs can be viewed as interacting with behavioral treatments, sometimes producing larger effects than either alone. Certain behavioral states (such as relaxation) may conceivably *increase* the effectiveness of certain antihypertensive drugs; conversely, certain drugs may increase the effectiveness of certain behavioral treatments. Developing the concept of synergistic pharmacological/nonpharmacological interactions is among the most exciting and important challenges for future behavioral medicine research.

Toxicity and Safety

The *therapeutic index* is technically expressed as toxic dosage$_{50}$/effective dosage$_{50}$. In the clinical setting, it refers to the ratio of response to reaction, and thus reflects the *selectivity* of the drug for positive vs. adverse effects. The slope of the dose-response relation becomes a measure of the *dose range* or *margin of safety*, to the extent similar to potency, i.e., it is the "potency for drug reaction." Toxic effects may be the extension of therapeutic or neutral effects into a toxic range, or simply adverse effects of any sort. *Side effects* are defined as effects other than those in the *primary reference* (the effects which justify the administration of the treatment to begin with, and which define clinical improve-

ment). Although not often recognized as such, side effects can be either positive, neutral, or negative in clinical value. A side effect can result from the *same* therapeutic action (i.e., occurring in tandem with the effect in reference) or it can be due to another action of the same drug. The concept of selectivity implies that drugs *always* have side effects.

The safety of a drug refers to the *clinical value* of adverse side effects and toxicity. Hence issues of *safety* can diminish and limit clinical effectiveness. It should be recalled that *clinical effectiveness* by definition does not simply refer to clinical effects in primary reference, but refers to the *balance* or ratio of positive to negative effects. Hence, although a given drug may produce major clinical effects (high positive efficacy) in the primary referent, if it is unsafe (producing reactions) it will not be classified as a clinically effective drug. In essence, the definition of clinical effectiveness requires the computation of a cost/benefit ratio.

Biobehavioral Considerations

Matters of safety, for which data are rather meager, are not well defined in current behavioral literature. While most procedures appear fairly innocuous, the most dangerous effect of such treatment of hypertension may be a lapse in appropriate medical care and drug therapy. Still, the range of effects has yet to be observed, and a concern for side effects further emphasizes the concepts of pattern response and selectivity. It suggests that behavioral researchers should routinely look for side effects in their treatments where side effects are not defined simply as negative reactions *but as positive or neutral responses as well.* In this regard, as mentioned above, Benson's relaxation procedure may have more side actions and side effects than blood pressure biofeedback, which may or may not increase its clinical effectiveness.

Phases of Clinical Research: Evaluation of Treatments

As indicated above, the methodology of pharmacotherapeutics must go beyond the observation of a drug's isolated physiological effects. Ultimately, a value must be placed on the utility of the drug, and the hypothesis of *clinical effectiveness* must be tested. For this purpose has evolved the conceptual framework of clinical outcome research. All data available from prior research relating to the drug enter the equation: from initial observations of response phenomena in animals and man to assessment of drug effects in diseased man. From this information the *indications* (circumstances of choice) and *contraindications* (circumstances of rejection) can be discerned. The factors relevant to this evalua-

tion, none of which can be omitted, are summarized again: (1) drug effects, (2) clinical efficacy, (3) selectivity, (4) safety, (5) patient responsivity, (6) patient reactivity, (7) net cost, and (8) net benefit.

Five phases of research are needed before the widespread usage of a drug occurs. In a ***preclinical investigation*** phase, in lower animals, basic properties of the drug's actions and physiological effects are observed and assayed. Clinical research proceeds through phase I, II, and III trials, while phase IV is currently proposed but not formally required:

Phase I trials are those in which individual patients or groups of patients receive the drug to determine its basic physiological effects, its dose-response relationship, and its side effects.

Phase II trials are those in which controlled comparisons are made of drug to placebo or other agents, in small groups of patients, usually with double-blind techniques, with further establishment of dose and toxicity. Tentative conclusions of cost/benefit are made.

Phase III trials are broad clinical trials in large populations of patients essentially duplicating the circumstances when the drug is released to the prescribing practitioner. Cost/benefit, clinical effectiveness evaluation is concluded.

Phase IV trials are proposed long-range epidemiological studies of the drug treatment in actual clinical practice.

Biobehavioral Considerations

Research on behavioral approaches to the treatment of hypertension are for the most part ***phase I trials*** (reviewed in A. P. Shapiro *et al.*, 1977). With the exception of a few phase II trials (e.g., Black and Cott, 1977; Patel, 1977; Surwit and Shapiro, 1977; Frankel *et al.*, 1978), the research has been of a demonstrational nature. Even at phase I, research has not been conducted with the goal of answering the several questions typically addressed in comparable drug experiments. Furthermore, there have been relatively few preclinical investigations of basic mechanisms, dose-response, toxicity, and so forth (reviewed in Harris and Brady, 1977). The value of recognizing the present status of research lies in the formulation of the research questions which remain before meaningful and responsible conclusions about clinical effectiveness can be drawn. Only from such contextual formulations can medically oriented researchers, and funding agencies, encourage progress into phase II trials. Present data are no more than suggestive, if encouraging, observations, and widespread use of behavioral treatments in hypertension is *not* yet justified.

Other Biobehavioral Considerations

Pharmacologists are concerned with specifying, as precisely and as completely as possible, the agent(s) in question. This includes assessing the agent's

physical properties, determining the procedures for obtaining and purifying the drug, and assaying its effects. In examining the behavioral literature, the first question is "how definable and reproducible are the behavioral methods themselves?" In other words, how definite and reproducible are the behavioral "agents" that make up a behavioral intervention? Environmental manipulations *per se* are often confused with the desired actions and effects that such agents should have, namely, the cognitions and behavior to be generated. In pharmacological terms, cognitions and behaviors are not "agents" but effects, even though their generation and continued practice may be necessary to produce the desired clinical response.

More effort is needed in specifying the total *set* of environmental *agents* that the person is exposed to, including not only the specific *instructions* used (the visual, auditory, and kinesthetic *stimulation* that the person is asked to process) but also all the additional *stimulus* parameters that can contribute to the total response observed. The social setting, including the appearance and behavior of the therapist, can be key interactive agents (if not the *major acting agents*) ultimately contributing to the observed clinical effects. More precise identification of the *environmental agents* enables consideration of what the *required intermediate effects* (behaviors) are for producing the desired clinical effects. This requires analysis of the total *pattern* of such intermediate effects. Davidson and Schwartz (1976) illustrate, for example, how different relaxation instructions require the generation distinct patterns of cognitive and somatic responses, leading to differential patterns of visceral change. In the pharmacological perspective, this illustrates how different sets of environmental agents (through simple instructions) can lead to the production of different central (level 5) and ultimately peripheral (level 4 and 3) effects, which over time can lead to the production of different sets of clinical effects. In this way, different relaxation instructions may produce different selectivities of actions and effects. Such subtle differences may or may not be more important to behavioral dynamics than behavioral therapeutics, a question yet to be answered.

The measurement of *agents* requires reliable and sensitive *assay* procedures, even though specific *procedures* for *behavioral assay* are not directly comparable to pharmacological ones. An attempt to improve assay procedures, including quality control, is called for at least on a *conceptual* level. Since many of the measurement procedures can be *interactive* with the agent and its effects, the problem of their interactional nature should be a concern of behavioral scientists as well. The classic Hawthorne effect and the experimenter bias effect in psychology are two illustrations of this problem (Rosenthal, 1967).

Even the basic procedures for assessing blood pressure in humans can themselves cause pressor or depressor effects. The iatrogenic effects involved in blood pressure measurements have already been noted (Pickering, 1974). The converse, as mentioned by Miller and Dworkin (1977), is that the measurement procedure may act as a cue for the person (via the CNS) to decrease his blood pressure *when it is being measured*, but not necessarily at other times. This

effect may be intentional (i.e., the patient deliberately lowers his pressure to please the therapist) or unintentional (i.e., the effect may be automatic, without the patient's awareness that he is generating the effect).

Concern for the absorption, biotransformation, and excretion of drugs is not closely analogous to behavioral treatments. However, in behavior treatments the external agents may be removed, but continued generation of behavior by the patient is required for long-term clinical effects. The concepts of *modulation* and *modification* provide an important clarification of this difference. Some drugs act by *modulating* the system (having effect so long as the drugs are present), as opposed to those producing a *modification* in the system (so that the presence of the drug is not needed to maintain the effect).

It is possible for a drug to have a modulating *action* on initial administration, yet have a *modifying effect* with continued administration. For example, a tranquilizer may modulate cortical activity (level 5), thereby reducing sympathetic activity (level 4), producing increased vasodilation (level 3), decreased peripheral resistance (level 2), and lowered blood pressure (level 1). On cessation of the drug, conditions may still be present for the pressure to rise again. However, if the pressure is maintained at a low level (an effect) for a sufficient period of time, it may lead to a resetting downward of the baroreceptors, and healing of "stiff" vascular beds. Consequently, when the tranquilizer is removed, the indirect effects of the sustained blood pressure control, with improved homeostasis, may allow the system to resist pressor stimuli. Thus the drug has *modified* the disease process.

This distinction between *modulation* and *modification* is applicable to behavioral therapies. Certain environmental manipulations are clearly modulatory in nature. One would suppose that the actions of the treatment are transient while the effects may be longer lasting only to the extent that biological modifications have occurred. On the other hand, certain aspects of behavioral procedures, especially those that lead to relearning, such as *modifications* in *lifestyle*, may be more permanent, even though the specific behavioral *agents* initiating the effects have been removed. This distinction helps clarify several problems concerning immediate effects vs. the maintenance of therapeutic gains, and the transfer of training outside the laboratory and clinic.

BEHAVIORAL DYNAMICS OF THE PLACEBO RESPONSE

The complexity of factors influencing the final pattern of effects produced by a drug has led to procedures in clinical pharmacology for controlling for "nonspecific" effects, i.e., those not immediately related to the chemical and physiological phenomena. The purpose of the "double-blind procedure" therefore is to maintain environmental conditions constant by manipulating only the "active"

components of the drug. The comparison thus consists of (1) active drug + environmental conditions (presumed to be random variables) and (2) placebo drug + environmental conditions. This design precludes assessment of environmental factors alone, unless a third, nontreatment control is included. Even then, the *interactive* role of the environmental factors *with* the active drug cannot be measured.

Although clinical pharmacologists by and large have been uninterested in the *interactive* role of environmental factors, their *conceptual* model clearly indicates the potential importance of such factors. The placebo response in hypertension provides one the best lines of evidence that environmental factors play a role in modulating and modifying the regulation of blood pressure (Wolf *et al.*, 1955). But while environmental factors are seen as sources of unwanted variance by some traditions, drug effects are seen similarly by traditional behavioral scientists. As mentioned previously, an *interactive* analysis indicates the importance of *both* sets of factors, if prediction of outcome in individual cases is to be possible. It also calls for interaction among traditions. (And since environmental conditions may be either synergistic or antagonistic to drug effects it becomes important to assess "placebo" factors in a positive rather than negative light.)

Social-psychological factors can be seen as potential agents that may modulate response to a drug, and research parameters developed in social psychophysiology have direct relevance in this regard. It is technically correct to classify biofeedback, psychotherapy, relaxation procedures, and the like as "placebo" treatment *if* it is recognized that by placebo we infer environmental and therefore behavioral intervention. What psychopharmacologists have called "set and setting" effects (respectively, CNS processes modulated by instructions and other environmental inputs, and the pattern of environmental agents present) can be seen as "side effects" and "placebo responses." Still, these are an *integral* part of the total response pattern, which is neither mystical nor invisible.

By classifying the total environment as a complex, "multidrug capsule," composed of many individual active ingredients, it becomes meaningful to analyze its components and their individual actions and effects, and then to consider their interactions in the clinical setting. It should become possible to determine which subcomponents, in which "doses," increase responsivity to particular drugs and to minimize psychosocial effects antagonistic to therapeutic success. Furthermore, the same conceptual procedures can be applied, optimizing environmental and behavioral manipulations as a means of regulating blood pressure. In the same way that social psychology and information processing have added to more sophisticated application of hypnosis (Hilgard, 1977), advances in understanding the placebo response can result. Although the placebo effect is often seen as "nonspecific," the effects of different components in the environment composing the placebo effect might be seen as highly selective. The foundation for progress lies in the integration of psychological and physiological

viewpoints, and recognition of anatomical pathways common to both. As recently stated by Gale *et al.* (1975):

> The best argument for social psychophysiology is that a good part of the repertoire of the nervous system was designed for purposes of social interaction. Thus, not only can psychophysiology provide the social psychologist with a unique running record of our emotional responses to other persons, but social interactions themselves provide an ecologically valid and appropriate context for the psychophysiological investigation of emotion. (p. 237)

By substituting "high blood pressure" for "emotion," an identical statement can be made for hypertension.

PATTERNS OF PRESSOR AND DEPRESSOR STIMULATION IN THE PATHOGENESIS AND TREATMENT OF HYPERTENSION

It is possible to evolve a comprehensive biobehavioral framework for integrating a biological systems analysis of blood pressure regulation and disregulation with the concepts underlying pharmacological approaches. The following analysis is offered with the goal of illustrating one possible structure.

First, one can view *all* types of hypertension as being produced by *multiple* (sets, patterns, mosaics) sources of *pressor* stimulation and/or the absence of multiple sources of *depressor* stimulation. The set or pattern of pressor and depressor stimulation will vary from person to person, but reflects the different *actions* of these stimuli.

Pressor stimulation can arise from numerous sources outside and inside the organism, affecting different sites of action. These sites may be at level 5 (CNS), level 4 (peripheral, neural, and humoral systems), and/or level 3 (peripheral organs). Pressor stimuli can act as *modulating* agents or can actually lead to *modification* of the mechanisms regulating blood pressure. Psychosocial pressor stimuli from the external environment will *interact with* and thus be modulated by *all* levels of biological processes from the CNS (level 5) through the peripheral neural and humoral mechanisms (level 4) to the effector organs (level 3), involving the various feedback mechanisms within and between levels 3 and 5, as well as level 2 (the hemodynamics) and level 1 (the final blood pressure itself).

The pressor stimuli may be classified in the following way, which could as well be applied to depressor stimuli.

1. Pressor stimuli outside the organism:
   a. Sensory stimulation: Sensory stimulation refers to environmental agents activating the five basic senses. Typically, sensory stimulation effects blood pressure via the central nervous system (level 5), but, as discussed previously, there are many steps in the chain from the sense organ (level 3 input organ) through the CNS (level 5) to the cardiovascular effector organ (level 3 output organ).

b. Organic or chemical stimulation: These stimuli include diet, drugs, bacteria, etc. Unlike environmental sensory stimulation, organic or chemical stimuli need not enter the system through level 3 input organs to modulate level 5 CNS process, since some may bypass levels 5 and 4 and act directly at level 3 output organs.

2. Pressor stimuli inside the organism: Stimulus sources may arise at various levels, from level 3 and 4 sensory input mechanisms, level 5 input, processing, and output mechanisms, and level 4 and 3 output mechanisms. Any may ultimately effect changes in blood pressure (level 1).

Level 5 *sources* of stimulation, particularly higher cortical and limbic structures, can generate *patterned* stimulation corresponding to images, perceptions, memories, emotions, etc. A monistic orientation integrating mind and brain (Luria, 1973; Schwartz, 1978) provides the framework for specifying how particular external stimuli (e.g., a telephone ring) may act to generate a complex set of level 5 cognitive stimuli, e.g., "worries and fears." These in turn activate other level 5 subsystems (such as the defense system in the hypothalamus), yielding patterns of sympathetic outflow (level 4). The sympathetic stimulation will provide changes in cardiovascular (level 3) as well as other level 3 organ processes. Increased blood pressure will be *one* of the complex patterns of effect seen at level 1.

Level 5 patterns of excessive pressor stimulation can also be initially programmed by genetic factors. These programs can be modulated (or, in certain cases, modified) by various lesions and other physical alteractions in the brain. These sources of stimulation can in turn modulate or modify the level 5 processing of external stimulation, and therefore interact with other psychological processes. As well, generation of level 4 and level 3 pressor stimuli by various genetic or disease processes can occur as sources of potential pressor stimulation. Altogether, high blood pressure (level 1) can be seen as a final reflection of a *total pattern* of pressor and depressor stimuli present at all higher levels (levels 3-5). However, the *actions* responsible for the high blood pressure can initially occur outside the organism, or involve any combination of levels within the organism. The blood pressure (level 1) at a given point in time is thus the *summating interaction* of all these stimuli.

The total pattern of pressor and depressor stimuli will vary from person to person, with different degrees of environmental, behavioral and biological factors contributing to the balanced regulation of blood pressure *in every case*. Schwartz (1977a) has previously outlined how stimulus conditions outside the organisms can shift the balance, leading to an instability of homeostasis which he calls disregulation, similar to Miller and Dworkin's (1977) notion of anti-homeostasis. In complex biobehavioral feedback systems, there are many points at which disregulation (thus high blood pressure) can occur. To uncover the specific conditions by which the system has become disregulated, a systematic biobehavioral diagnosis should be made which examines patterns of pressor and

depressor stimuli and their effects within the cardiovascular system, and within other systems as well.

Once stated in this fashion, it becomes clear that *all* therapies for hypertension, be they pharmacological, surgical, or behavioral, attempt to decrease the number and intensity of pressor stimuli, and increase the number and intensity of depressor stimuli. Ideally, different treatments and/or combinations of treatments would attempt to modify the pressor and depressor parameters in a manner specific to the diagnosis of the disregulatory patterns. In this way should be produced the most effective homeostatic response (Schwartz, 1977a).

If high blood pressure (level 1) is only *one* of the effects of environmental pressor stimulation, and if these are active in the disease processes, the isolated lowering of pressure by drugs without removing the *sources* (or active agents) of the pressor stimuli will lead to another disregulation, affecting systems involved in the *total* set of effects of the pressor stimuli. Thus the pharmacological model provides the best argument for directly treating the *source* of *action*, and thereby minimizing disregulation in other systems (Schwartz, 1977a). In other words, *the conceptual framework underlying clinical pharmacology provides the best justification for modifying environmental and behavioral factors for the total well-being of the patient.*

To systematically analyze and compare different behavioral treatment procedures, it is necessary to precisely classify what combination of external agents and level 5 CNS processes is involved in each therapy package. As indicated above, the selection of a given behavioral treatment or combination of treatments (including drugs) should ultimately be dictated by a detailed diagnosis that assesses the pattern of external and internal pressor stimuli present in the individual. The combination of pharmacological and behavioral treatments should ideally match the array of pressor stimuli present with the goal of removing or reducing them. Similarly, selecting procedures which accentuate depressor stimuli from the external environment (e.g., pleasant scenery) or internal environment (e.g., "thinking happy thoughts") or electrical stimulation of the baroreceptors could also be considered.

This framework presents an ideal goal, one that cannot be reached by either current measurements, by treatment, or by available procedures. However, the limitations in current *methods* should not restrict the *conceptual* goals. When the conceptual goals are defined purely in terms of present limitations, false dichotomies between conceptual models (i.e., pharmacological vs. behavioral) occur, hampering both research and clinical practice. The present analysis illustrates how biobehavioral systems theory combined with the conceptual framework of pharmacology provides a means for integrating behavioral and biological orientations into a general behavioral medicine framework.

SELF-REGULATION OF BLOOD PRESSURE IN BIOLOGICAL PERSPECTIVE

The conceptual framework underlying the pharmacological sciences recognizes the important interaction of person and agent in determining the total set of actions and effects of the individual. Unfortunately, this orientation has not, until very recently, been put into practice. Consequently, drugs have been studied and prescribed as agents administered to passive organisms. However, as is particularly evident in the area of "therapeutic compliance," treatment ultimately involves self-regulation.

From a biobehavioral systems perspective, self-medication can be seen as but one aspect of self-regulation. In fact, if other environmental stimuli, such as radios, televisions, and books, are classified as "agents," then a person's self-determination to engage in *any* activity involving the reception of psychological or chemical agents can be seen as a biobehavioral process of self-regulation. The movement in the behavioral sciences toward understanding the psychobiological mechanisms underlying self-control has broad implications for all treatments in psychology and medicine (Schwartz, 1978).

The excitement engendered by the research on biofeedback is partly based on the demonstration that selective self-regulation of cardiovascular processes can be achieved in the average person. This capacity for cardiovascular self-regulation is not so startling however, when cardiovascular regulation is considered within a biobehavioral systems framework. Simply stated, behavioral or cognitive self-regulation *always* involves cardiovascular self-regulation, even though its regulation is typically not consciously recognized by the person.

Biofeedback, as a biobehavioral research and conceptual tool, is designed to increase the capacity for cardiovascular self-regulation. Although not widely recognized, feedback is ultimately involved in all treatments, including drug treatments (see Schwartz, 1978). Physicians select and modify the types and dosage of treatments based on the feedback they obtain of the patient's blood pressure. The major difference in biofeedback-oriented treatment is that it places more of the responsibility for environmental (including chemical) and behavioral regulation within the patient, which is the ultimate goal of self-regulation procedures. From this perspective the correction of biobehavioral disregulations in hypertension always utilizes "biofeedback" in one form or another. Self-medication, diet modification, exercise, etc., become part of a broader psychobiological concept of self-regulation and self-care.

Although the conceptual framework underlying the pharmacological sciences is consistent with this point of view, it is unfortunately not emphasized in research training or clinical practice. We believe that the development of this

framework by scientists concerned with the integration of behavioral and biological approaches to cardiovascular health and disease is a major challenge for the future.

SUMMARY AND CONCLUSIONS

In this article we have explored the theoretical foundations of behavioral and pharmacological treatment approaches to hypertension. We have offered suggestions for conceptualizing the pathogenesis of hypertension from a biological systems approach and viewing behavioral treatment of hypertension from the viewpoint of clinical pharmacology. Historically, separation of behavioral and pharmacological approaches fostered independent and parallel development in these areas; however, their more active integration now seems appropriate for a truly comprehensive approach to the management of patients with high blood pressure. A biobehavioral systems approach which recognizes the role of the central nervous system (level 5) in the coordination and regulation of blood pressure provides a foundation for this integration.

Given the relative youth of the behavioral sciences, the majority of behavioral models have been restrained from certain practical questions in biomedical research, such as the need to uncover behavioral mechanisms involved in regulation of blood pressure and to develop techniques for comparison of clinical effectiveness with pharmacological forms of treatment. By consideration of research in pharmacodynamics and pharmacotherapeutics, we have attempted to clarify important misunderstandings between behavioral and pharmacological researchers in hypertension. Further, we have illustrated how meaningful parallels can be drawn between pharmacology and psychology, and have discussed behavioral dynamics and behavioral therapeutics in this light.

Pharmacological researchers, on the other hand, have been remiss in ignoring behavioral factors contributing to the action and the effects of drugs; a "disdain" (Benson and Epstein, 1975) or mystical view of "placebo" responses has been too common. But, ironically, the conceptual framework of clinical pharmacology actually provides its own argument and rationale for a systematic view of placebo effects as behavioral "side effects" which reflect important environmental and behavioral input to the regulation of blood pressure.

It is fascinating to consider how recent advances in *biology* may provide the rationale for investigating *behavioral* aspects of the treatment of disease (Cohen and Obrist, 1975; Jenkins, 1976a,b; Schwartz, 1977d). Until quite recently, as biological mechanisms of disease were uncovered, investigators simply assumed that direct biological intervention alone was indicated. Likewise, when psychological factors were found to be related to disease, investigators simply assumed that the "direct" manipulation of these "mental" processes was called

for, but in an abiological manner. Hence the mind/body dichotomy was thus perpetuated. Clearly, a rapprochement is needed. The split between behavior and cognition in the behavioral sciences has had a similar history, and, interestingly, it is developing a similar rapprochement. As stated by Bandura (1977) in his model of self-efficacy, it is possible to posit that all behavioral interventions involve cognitive mechanisms, yet at the same time to argue that the best way to produce changes in cognition is through the modification of behavior. In other words, modern cognitive theory is being used as a justification for behavioral modification!

It is now recognized that the neurophysiological mechanisms that subsume cognition, memory, emotion, and behavior, and therefore personality, can be, in many cases, effectively modulated or modified by environmental and behavioral procedures. Current research documenting the role of the central nervous system in cardiovascular regulation and disease provides *biological* justification for considering *environment* and *behavioral* factors in the etiology and treatment of hypertension. That the central nervous system acts as a common pathway, integrating environmental and behavioral factors on the one hand and peripheral cardiovascular dynamics on the other, is an important concept for the emerging field of behavioral medicine (Schwartz, 1978). It follows that behavioral therapies, including group and family therapies, can be reconceptualized as psychobiological therapies having psychobiological consequences.

A view of hypertension as a multifaceted biobehavioral manifestation of disregulation (Schwartz, 1977a) has a number of advantages. High blood pressure is a unitary disease only in the sense that it contributes to a specific, characteristic pathophysiology. Although traditional medical treatment is ultimately aimed at lowering blood pressure (level 1), by producing pharmacological or surgical alterations at the peripheral organs (level 3), it does not necessarily follow that the mechanisms by which the level 3 processes became disregulated is the same from case to case. Simply stated, hypertension is not a unitary disorder. Specification of the pattern of pressor and depressor stimuli contributing to pathogenesis in a given patient further emphasizes the importance of understanding how environmental conditions interact with biology. In this respect, all treatments, be they primarily behavioral, surgical, or pharmacological, influence blood pressure.

A major difficulty in implementing a biobehavioral systems perspective is that it proposes the measurement of multiple parameters that cut across behavioral and biomedical disciplines. It is unreasonable to expect that any one investigator will be able to master all the relevant components. However, as the different disciplines develop a common framework for integrating behavioral and biomedical approaches to health and illness, the road will be paved for more comprehensive, interdisciplinary research and application. As theory becomes more integrative, and as behavioral and biomedical measurement techniques

improve, there will be an increasing need to use multivariate techniques to statistically analyze behavioral medicine data.

Behavioral and biological approaches to treatment need not be seen as operating under different conceptual models, but rather as affecting various levels within or relevant to the cardiovascular system. This unitary view holds the promise of stimulating more systematic descriptions of the pattern of agents and mechanisms involved in behavioral and pharmacological treatments, and can lead to therapeutically optimal application of these *interactions* (the synergistic combinations of behavioral and biomedical procedures) as the cornerstone of a behavioral medicine analysis (Schwartz and Weiss, 1978).

NOTE ADDED IN PROOF

A comprehensive and wide ranging biobehavioral systems model has recently been published by Miller (1978). A useful introduction to Miller's theory as applied specifically to behavioral medicine is provided by Schwartz (1980).

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Reprinted by
U.S. Department of Health and Human Services
Public Health Service, National Institutes of Health

*U.S. GOVERNMENT PRINTING OFFICE : 1980 O-311-201/313